CLINICAL PROFILE OF CUTANEOUS VASCULAR ANOMALIES AND THE ASSOCIATED OVERGROWTH SYNDROMES

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE RULES AND REGULATIONS FOR THE M.D. BRANCH XX (DERMATOLOGY, VENEREOLOGY AND LEPROSY) EXAMINATION OF THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY TO BE HELD IN APRIL, 2017

CERTIFICATE

This is to certify that the dissertation entitled “Clinical profile of cutaneous vascular anomalies and the associated overgrowth syndromes ” is the bonafide original work of Dr.Raja Sekhar.M.

This study was undertaken at the Christian Medical College and Hospital, Vellore from September 2014 to July 2016, under my direct guidance and supervision, in partial fulfilment of the requirement for the award of the MD degree in Dermatology, Venereology and Leprosy of the Tamil Nadu Dr. M.G.R. Medical University.

Guide & Head of the Department

Dr. Renu George
Professor & Head,
Department of Dermatology, Venereology & Leprosy,
Christian Medical College, Vellore

CERTIFICATE

This is to certify that the dissertation entitled “Clinical profile of cutaneous vascular anomalies and the associated overgrowth syndromes ” is the bonafide original work of Dr.Raja Sekhar.M.

This study was undertaken at the Christian Medical College and Hospital, Vellore from September 2014 to July 2016, under my direct guidance and supervision, in partial fulfilment of the requirement for the award of the MD degree in Dermatology, Venereology and Leprosy of the Tamil Nadu Dr. M.G.R. Medical University.

Principal

Christian Medical College

Vellore

DECLARATION

This is to certify that the dissertation entitled, “Clinical profile of cutaneous vascular anomalies and the associated overgrowth syndromes ” is the bonafide work of Dr.Raja Sekhar.M towards the M.D. Branch (Dermatology, Venereology and Leprosy) Degree examination of the Tamilnadu Dr. M.G.R Medical University, to be conducted in April 2017.

Guide

Dr. Renu George,

Professor and Head of the department,

Department of Dermatology, Venereology and Leprosy,

Christian Medical College Hospital,

Vellore – 632 004.

DECLARATION

This is to declare that the dissertation entitled, “Clinical profile of cutaneous vascular anomalies and the associated overgrowth syndromes”, in the department of Dermatology, Venereology and Leprosy is my original work, done under the guidance of Dr. Renu George, Professor and Head of Department of Dermatology, and submitted in partial fulfilment of the rules and regulations for MD degree Branch XX (Dermatology) of the Tamil Nadu Dr. M.G.R. Medical University, Chennai to be conducted in April 2017.

Raja Sekhar.M,

Post graduate,

Christian Medical College,

Vellore.


Turnitin Document Viewer - Mozilla Firefox
https://turnitin.com/dv?o=710426308&u=1055582380&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical ...
2015-2015 plagiarism - DUE 07-Nov-20
Originality
GradeMark
PeerMark
Clinical profile of vascular anomalies and the associated overgrowth syndromes
BY (NULL)
turnitin
6%
SIMILAR
--
OUT OF 0
INTRODUCTION
Vascular anomalies represent a wide spectrum of disorders ranging from isolated vascular nevus to disabling and life threatening entities.(1) They are the disorders affecting endothelium of any part of vasculature (capillaries, veins, arteries, or lymphatics) which result from the defect of angiogenesis and vasculogenesis during embryonic development.(2) Since the biological classification proposed by Mulliken and Glowacki in 1982 was introduced there has been significant progress in understanding the nature of these disorders and their treatment.(3) In the past many of these disorders were misdiagnosed due to confusion in nomenclature. The binary classification of Mulliken and Glowacki divided vascular anomalies broadly into two distinct entities, vascular tumours and vascular malformations which washed out most of the confusion regarding terminology of vascular anomalies.(4) With this background, International Society for the Study of Vascular Anomalies (ISSVA), in 1996, proposed a basic classification system to provide a common platform. This was further updated to provide the recent ISSVA classification of vascular anomalies which was adopted in 2014.(5)
The estimated prevalence of cutaneous vascular anomalies from the West is
Match Overview
1 Garzon, M.C.. "Vascula... Publication 1%
2 www.e-ijd.org Internet source <1%
3 Hemangiomas and Vas... Publication <1%
4 Liang, Marilyn G., and I... Publication <1%
5 www.science.gov Internet source <1%
6 Hemangiomas and Vas... Publication <1%
7 www.neurosurgery-blo... Internet source <1%
8 pediatrics.aappublicati... Internet source <1%
PAGE: 1 OF 31
Text-Only Report
12:54 PM
28/09/2016

ACKNOWLEDGMENTS

First and foremost I would like to express my heartfelt sincere gratitude to my teacher and guide Dr. Renu George for her immense support, guidance and encouragement throughout this study. Without her active guidance, help, cooperation & encouragement, this dissertation wouldn't be a fruitful one.

I wish to thank Dr. Shyamkumar N Keshava, my co-guide for his immense help in guiding and completing this dissertation. His contribution in completion of this study is invaluable and thankworthy.

I extend my thanks to Dr.Lydia Mathew and Dr. Sunil Agarwal, co-investigators of this study for their guidance and recruitment of cases. I am also grateful to Dr.Vinu Moses, co-investigator of this study, for his timely help in selection of radiology images.

I also express my gratitude to Dr. Sivaranjini, Dr. Dharshini, Dr.Venkataraman, Dr.Ankan Gupta, Dr.Nirmal, Dr.Anu Anna George and Dr. Anjana, Assistant Professors, Dept. of Dermatology, for their valuable inputs and help in recruitment of patients.

I also like to thank Dr.Dincy Peter, Professor and Dr.Leni George for their timely support and Dr.Visali, statistician for her help in the statistical analysis

My special thanks to Dr. Priya kuryan, my senior for her timely help and constant guidance.

I thank my colleagues Drs.Rosemary, Parthiban, Rajam, Shivani, Anju, Jacquiline, Vipin Roy and all other post graduates for their constant support throughout this study.

I thank Mrs.Nithyavani for her exemplary secretarial assistance in completion of this study.

I express my sincere thanks to Mr. Lazarus Raj Premkumar for his help in photography and Mrs. Sheeba Tennyson for her help in getting histopathology slides.

I express my gratitude to all those who have directly or indirectly helped me to complete this study.

My special thanks to Mrs.Shashi Rekha, my wife and all other family members who have always supported me and appreciated my work wholeheartedly.

ABBREVIATIONS

AVF	Arteriovenous fistula
AVM	Arteriovenous malformation
BRBB	Blue rubber bleb syndrome
CAVM	Capillary arteriovenous malformation
CH	Congenital hemangioma
CLAVM	Capillary lymphatic arteriovenous malformation
CLOVES	Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, skeletal/scoliosis and spinal abnormalities
CLM	Capillary lymphatic malformation
CLVAVM	Capillary lymphatic venous arteriovenous malformation
CLVM	Capillary lymphatic venous malformation
CM	Capillary malformation
CM-AVM	Capillary malformation-arteriovenous malformation
CMTC	Cutis marmorata telangiectatica congenita
CNS	Central nervous system
CVAVM	Capillary venous arteriovenous malformation
CVM	Capillary venous malformation
DIC	Disseminated intravascular coagulopathy
GLA	Generalized lymphatic anomaly
GSD	Gorham-Stout disease
GVM	Glomuvenous malformation
HHT	Hereditary hemorrhagic telangiectasia
HOI	Hemangioma of infancy
IH	Infantile hemangioma / hemangioma of infancy

ISSVA	International society for the study of vascular anomalies
KHE	Kaposiform hemangioendothelioma
KLA	Kaposiform lymphangiomatosis
KMP	Kasabach-Merritt phenomenon
KTS	Klippel-Trenaunay syndrome
LM	Lymphatic malformation
LVM	Lymphatic venous malformation
MCAP	Megalencephaly-capillary malformation-polymicrogyria
M-CM	Macrocephaly-capillary malformation
MICCAP	Microcephaly-capillary malformation
NF	Neurofibromatosis
NICH	Non-involuting congenital hemangioma
PHACE	Posterior fossa malformations, hemangioma, arterial anomalies, cardiovascular anomalies, eye anomalies
PICH	Partially involuting congenital hemangioma
PPV	Phacomatosis pigmentovascularis
PROS	PIK3CA-related overgrowth spectrum
PWS	Port wine stain
RICH	Rapidly involuting congenital hemangioma
SWS	Sturge Weber syndrome
TA	Tufted angioma
VLM	Venolymphatic malformation
VM	Venous malformation
VMCM	Venous malformation cutaneo mucosal

CONTENTS

INTRODUCTION

Vascular anomalies represent a wide spectrum of disorders ranging from isolated vascular nevus to disabling and life threatening entities.(1) They are the disorders affecting endothelium of any part of vasculature (capillaries, veins, arteries, or lymphatics) which result from the defect of angiogenesis and vasculogenesis during embryonic development.(2) Since the biological classification proposed by Mulliken and Glowacki in 1982 was introduced there has been significant progress in understanding the nature of these disorders and their treatment.(3) In the past many of these disorders were misdiagnosed due to confusion in nomenclature. The binary classification of Mulliken and Glowacki divided vascular anomalies broadly into two distinct entities, vascular tumors and vascular malformations which washed out most of the confusion regarding terminology of vascular anomalies.(4) With this background, International Society for the Study of Vascular Anomalies (ISSVA), in 1996, proposed a basic classification system to provide a common platform. This was further updated to provide the recent ISSVA classification of vascular anomalies which was adopted in 2014.(5)

The estimated prevalence of cutaneous vascular anomalies from the West is 4.55%.(6) There is a paucity of data on cutaneous vascular anomalies from Asia (7,8) and in particular the Indian subcontinent.(9,10) As published studies on vascular anomalies are hospital based, the true prevalence of cutaneous vascular anomalies in India is not known.

AIMS

OBJECTIVES

Primary objective:

To study the clinical features of cutaneous vascular anomalies.

Secondary objective:

To describe the overgrowth syndromes and extracutaneous features of vascular anomalies.

REVIEW OF LITERATURE

Vascular anomalies represent abnormalities that results due to the defect in angiogenesis and vasculogenesis during embryogenic development.(11) The 2 types are vascular tumors and vascular malformations as per the binary classification of Mulliken and Glowacki (1982).(3) Based on this, in 1996 , International Society for the Study of Vascular Anomalies (ISSVA) made a basic classification system to provide a common language.(12) From then on the classification has been updated with inclusion of new entities keeping the basic binary classification same. The main distinction between two groups is the cellular proliferation. Vascular tumors have mitosis and vascular malformations do not have mitosis but results due to dilatation of vessels.(3) Hemangiomas are divided into infantile hemangiomas(IH) and congenital hemangiomas(CH) [(rapidly involuting congenital hemangiomas(RICH) and noninvoluting congenital hemangiomas(NICH)] depending on the age of onset. (4) Vascular malformations are divided based on the type of vessel involved.

Detailed ISSVA classification of vascular anomalies 2014 is given in [**Annexure I (A)**].(5)

Epidemiology

Most of the epidemiological studies on vascular anomalies have been done in the Western countries like USA and Canada.(2,13–15) The estimated prevalence of

vascular anomalies in population is 4.55%.(6) In these countries, vascular tumors constitute 30%-60% and vascular malformations constitute 30%-70% of all vascular anomalies. Similar studies were done in India but with smaller sample sizes.(9,10) In two retrospective hospital based studies from India including 20 patients and 19 patients respectively, the prevalence of vascular tumors and malformations was 10% & 90% in the first study and. 89.5% & 10.5% in the second study.(9,10)

Age distribution

The age distribution of vascular tumors and vascular malformations differ according to the specific type. Infantile hemangioma or Hemangioma of infancy (HOI),the most common vascular tumor does not occur at birth, but appears within first few days after birth.(16,17) However the precursor of HOI can be evident at birth. Congenital hemangiomas and most of the other vascular tumors except HOI appear at birth. Although most of the vascular malformations are present at birth they can be apparent at any age.(18)

Gender distribution

Many epidemiological studies have confirmed that vascular tumors, especially hemangiomas have significant female preponderance with female to male ratio of 1.7 :1 to 2.4 : 1.(16,19,20) Vascular malformations have more or less equal gender distribution.(21)

Vascular tumors

In a large epidemiological study done on 5620 patients, 85.9% were IH, 6.3% were KHE, 5.4% were congenital hemangiomas and 2.4% were others.(2)

Infantile Hemangiomas (IH)

Epidemiology: IH is the most common vascular tumor in childhood with a prevalence of 3%-10% in infants.(18,19) In two studies on pediatric dermatoses reported from South India, the number of patients with hemangiomas constituted 0.5% in one study(22) and 0.44% in the second.(10) They constitute for about 85% of all vascular tumors.(2)

Clinical profile: IH is apparent between 2 weeks to 2 months, grow rapidly in first 6 months of life, involute with time and do not infiltrate much. In a large case-control study, the site of occurence of IH was as follows: head and neck- 69%, trunk-17%, extremities-13% and perineum-4.5%.(19) Chiller KG et al, have proposed the division of IH into localized, segmental, indeterminate and multifocal. Data from their study were as follows: localized-72%, segmental-18%, indeterminate-8% and multifocal-3%. They found that segmental hemangiomas were mostly associated with developmental abnormalities, more complications, poor outcome and were common among Hispanic infants.(16) It has been reported that 80% of hemangioma size was reached among IH within first 3 months of age.(23) Segmental hemangiomas and deep hemangiomas had continued growth beyond 3 months of age and associated with complications which need proper follow up.(23)

Risk factors: Multiple case studies have shown that IH are more common in females, Caucasians, premature and low birth weight babies, products of multiple gestations, maternal pre-eclampsia, placental abnormalities, medication use like antibiotics, antifungals, Chinese herbal medicines, progesterone, oral contraceptive pills, NSAIDS and those who have undergone chorionic villus sampling.(18–20, 24)

Complications: High risk clinical indicators include centrofacial, perioral, periorbital, perinasal involvement, segmental hemangiomas with size >5cm over face, lumbosacral/ perineal areas, thick/bulky lesion over face and early white discoloration. Intermediate risk indicators are lateral face, scalp, hands, feet, body folds (neck, axilla), segmental with size > 5cm over trunk, arms and legs. Low risk indicators include small hemangiomas localized to unexposed areas of trunk and extremities.(25) In a prospective study done in 7 US pediatric dermatology clinics on 1058 consecutive children with IH, 24% children experienced complications related to their hemangiomas. Ulceration was the most common complication (16%) followed by visual impairment (5.6%), airway obstruction (1.4%), hearing impairment (0.6%) and cardiac compromise (0.4%). Lesions on the face, segmental morphology and large size were predictors of complications.(26)

Diagnosis: IH can be diagnosed by proper history and clinical examination. Biopsy with GLUT-1 stain is useful for confirmation of diagnosis and also to differentiate from other vascular proliferations and malformations.(27,28) Doppler US of IH shows high flow within well defined solid mass along with arterial and venous waveforms.(18) MRI scans are done to delineate the extent of the lesion especially if the lesion is adjacent to vital

structures. MRI shows bright signal on T2W with internal high flow voids.(18) Ultrasound abdomen is useful to look for hepatic hemangiomas in cases of multiple hemangiomas. Thyroid function should be tested in case of hepatic hemangiomas as they are associated with hypothyroid state.(29)

Syndromes associated with infantile hemangiomas

A subset of infantile hemangiomas are associated with structural abnormalities and are broadly categorized into two syndromes based on location of hemangioma and other associated clinical findings.(30)

PHACE(S) syndrome: It stands for posterior fossa abnormalities, hemangiomas of the face, arterial anomalies, cardiac anomalies, coarctation of aorta, eye abnormalities and sternal clefting / supraumbilical raphe.(31) PHACE syndrome has strong female predominance. Consensus statement for diagnostic criteria of PHACE syndrome was developed in 2009.(32) [**Annexure I(B)**] In a multicenter prospective study on 108 patients with large facial hemangiomas, the prevalence of PHACE syndrome was 31%. Upper face hemangiomas (fronto-temporal and fronto-nasal segmental) were commonly associated with PHACE syndrome. More than 90% of patients had more than one extra-cutaneous finding. The most common extra-cutaneous findings were arterial anomalies of CNS (91%) and cardiac anomalies (67%).(33) Investigations required in suspected case of PHACE syndrome include MRI/MRA of head and neck, echocardiogram and ophthalmological examination.(34)

LUMBAR syndrome: This syndrome constitutes lower body hemangiomas along with associated group of structural abnormalities. LUMBAR syndrome stands for lower body infantile hemangiomas, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies and rectal anomalies.(30,35) Plain X-rays of lower extremities, duplex and MRI/MRA scans of spine, abdomen, pelvis and lower extremities are needed for evaluation of LUMBAR syndrome based on regional location of IH.(35)

Congenital hemangiomas (CH): Congenital hemangiomas are uncommon vascular tumors in contrast to IH. In a retrospective review of 6459 children with vascular anomalies, 14.1% of children had CH.(8) Based on natural history, CH are divided into a)Rapidly involuting congenital hemangioma (RICH)**,** b**)**Non-involuting congenital hemangioma (NICH) and c)Partially involuting congenital hemangioma (PICH)

Clinical features: They present at birth in fully grown status. They present as a thick plaque or exophytic mass over head, neck or extremities.(36) The involution of RICH is in the early neonatal period and completes by 14 months. Rarely involution of RICH may occur in utero.(37) NICH has same features as RICH but presents as less exophytic mass. In a retrospective study on 30 patients of NICH, trunk and extremities were most common sites.(38) NICH do not involute spontaneously and even grow proportionate to child growth.(30) PICH has features of both RICH and NICH. Nasseri et al described 8 cases of CH that behaved as RICH initially with involution in first 12-30 months and later stabilized in size and appearance as NICH. All eight children were full-term healthy

children.(39) Complications of CH are ulceration, bleeding and high output cardiac failure which are associated predominantly with large hemangiomas.(40) Transient thrombocytopenia and coagulopathy are found in RICH.(41)

Diagnosis: CH are differentiated from IH based on presence of fully grown vascular tumor at birth. RICH and NICH are differentiated based on natural history of involution. CH are diagnosed clinically in most instances. Ultrasound and MRI findings of CH often overlap with that of IH. Doppler US shows well defined solid mass with internal vascularity whereas MRI shows high-intensity flow enhancement and internal high flow voids.(18,42) There are few radiological differences found between CH and IH in terms of high heterogeneity, visible vessels and calcifications that are predominant in CH.(18,42) CH may even diagnosed in utero.(43)

Tufted angioma (TA): It is one of the rare benign vascular tumors and appears at infancy or during early childhood. Jones and Orkin in 1989 first described the condition and suggested the name ‘tufted angioma’ as the histopathological picture showed multiple discrete angiomatous tufts and lobules scattered in dermis giving a “cannon ball” appearance. (44) TA shows a clear male predominance and presents as dusky red to violaceous indurated plaques with hypertrichosis and hyperhidrosis of the overlying skin in some patients. Most common site involved is the limbs. TA may be associated with Kasabach-Merritt phenomenon, and with chronic coagulopathy but without thrombocytopenia.(45)

Kaposiform hemangioendothelioma (KHE): It is a locally aggressive vascular tumor that occurs frequently during infancy and early childhood.(46) KHE shows a slight male predominance (male to female ratio= 1.33: 1). One study showed that 93% of cases occurred in infancy and appeared as enlarging subcutaneous mass with purpuric/bruised appearance and 11% of patients had extracutaneous locations.(47) Most of the lesions were deep and the sites involved in order of frequency were extremities followed by the trunk and then the head and neck region. Retroperitoneum was the commonest extracutaneous site. Retroperitoneal lesions, intrathoracic lesions and deeper lesions infiltrating muscles were found more likely to manifest Kasabach-Meritt syndrome (KMP).(47) Histopathological examination of KHE shows coalescing lobules or sheets of tightly packed spindle cells in infiltrating dermis, fat and connective tissues.(46)

Kaposiform lymphangiomatosis (KLA): It is a newly described lymphatic anomaly that has features of both tumor and malformation. It is a distinct entity and differs from KHE in clinical behaviour and imaging features. There is a male predominance. The common presentations were respiratory symptoms (50%), hematological abnormalities (50%) and palpable enlarging mass (35%). All patients had intrathoracic involvement with pericardial effusion and/or pleural effusion. Bone and spleen were the common extrathoracic sites involved. Vertebral bones were the most common bones involved.(48) It also exhibits KMP as in KHE, but with less severe thrombocytopenia. Radiological imaging like MRI and duplex scan are to be done to detect and delineate the lesions as it is diffuse and multifocal.

Vascular malformations

Epidemiology: The incidence of congenital vascular malformations is 0.3 – 1.5%.(49) Vascular malformations are divided based on the flow velocity (slow flow/ high flow) and the type of vessel involved (capillary, venous, lymphatic, arterial or combined).(3) In a large epidemiological study involving 5620 patients, the statistics of various malformations were as follows: capillary malformations-11%, venous malformations-36.8%, lymphatic malformations-28.3%, arteriovenous malformations-14.3% and combined malformations-9.6%.(2)

Clinical profile: Vascular malformations are present since birth, but they may become apparent after few months or years after birth.(18,50) Vascular malformations are slow growing, infiltrative, do not regress and continue to expand with time.(18) They do not have a growth phase and involution phase like hemangiomas.(49) They may occur anywhere on the body. Their occurrence in head & neck region is a source of functional & aesthetic compromise.(51) In a study done on 175 consecutive patients, 56% of vascular malformations were found at birth,87% of patients had symptomatic vascular lesions (pain-51%, functional compromise-27%, swelling-24%, disfigurement-21%). Patients with lesions over the extremities were likely to experience pain.(13)

Diagnosis: Most of the vascular malformations can be diagnosed by thorough history and physical examination. But the role of radiological studies comes into play in situations where extra cutaneous features are associated with vascular anomalies. They are useful in the differentiation of vascular malformations, to know the extent of lesions

and for pretherapeutic evaluation.(18,52) Doppler US of vascular tumours shows fast flow within the lesions which differentiates from slow flow vascular malformations. It also shows no or minimal arteriovenous shunting that differentiates vascular tumours from AVM.(53) MRI and CT could be used further to know the extent of the vascular anomalies before the treatment.(53) Flow velocity of vascular malformations can also be studied .(54)

Capillary malformations

Clinical profile: Capillary malformations present on skin as port-wine stains (PWS). They have wide spectrum of presentation ranging from small and localized to large and covering multiple areas of body.(21,49) They appear anywhere on the body although frequently found in head and neck region.(55) Capillary malformations can involve one or two facial dermatomes determined by trigeminal nerve innervation. The order of frequency of involvement is V2 (57%) followed by V3 and V1 dermatomes.(49) As the age of the patient increases, the color of the lesion deepens from pink to purple and nodular hyperplasia and thickening also increase with age. This is predominantly common over the areas supplied by second and third trigeminal nerve branches.(56) It is also reported that the patients associated with glaucoma and mental retardation have large PWS involving more facial area than those lacking these conditions.(55) There are few reports of acquired PWS which develops later in life. This is an uncommon entity and less than 75 cases have been reported in literature.(57) Various triggering factors have been proposed including trauma, sun exposure, isotretinoin, oral contraceptive pills,

statins and metformin.(58–60) In a review of 59 cases of acquired PWS, trauma was the most common antecedent factor which was found in 17% of cases with slight female predilection.(58) The proposed mechanism of acquired PWS are alteration in capillary neural tone or dragging of attention of patients/guardians after an antecedent trauma.(58)

Genetics : Somatic GNAQ mutations were found in 100% of SWS patients (9 of 9) and 93% of nonsyndromic PWS patients (12 of 13) in one study.(61)

Diagnosis: Capillary malformations are diagnosed based on clinical findings. Sometimes Doppler and MRI scans are needed to differentiate from the cutaneous erythema of Schoebinger stage 1 AVM.(53)

Cutis marmorata telangiectasia congenita (CMTC): CMTC is a distinctive cutaneous vascular malformation that resembles physiological cutis marmorata. It presents as localized or generalized fixed reticulated vascular pattern. It is usually sporadic and majority of cases are found at birth. A female preponderance has been reported.(62) Limbs are the most common sites involved with two third cases being unilateral.(63) Most common associated finding is limb asymmetry which may be limb hypoplasia, hyperplasia or both. The other associated findings include capillary malformations, glaucoma, aplasia cutis, cleft palate and hydrocephalus.(62)

Venous malformations (VM)

Clinical profile: Venous malformations are the most frequent congenital vascular malformations referred to vascular anomaly centers.(2) In general VM presents

sporadically although familial cases have autosomal dominant inheritance.(49) They can be localized or extensive. Usually lesions occurring in extremities are localized or segmental and those of head and neck region are extensive than their initial presentation.(21) VM can occur not only in skin and subcutaneous tissue but also in internal organs, bones, skeletal muscle etc. They present as bluish soft compressible masses and increase in size with crying or other Valsalva maneuvers.(52) No thrill or bruit is observed in VM. Their main locations are the head and neck (40%), extremities (40%) and trunk (20%).(64) Complications of venous malformations are not uncommon. Pain localized to the lesion is the most common complication. It occurs mostly over the lesions of extremities which are thrombosed. Phleboliths occur as the consequence of calcification of the thrombosis in malformed venous channels.(65) Abnormal coagulation profiles occur due to localised intravascular coagulation (LIC), frequently described in venous malformations. It is associated with large or extensive, deep VM and palpable phleboliths.(66) Venous malformations of head and neck may cause mechanical obstruction or compression of various vital structures depending on their location and extent. Cosmetic disfigurement is the other psychosocial complication related to VM of head and neck.(67)

Investigations: Elevated d-dimer is the most common coagulation abnormality detected among patients with venous malformations. It is associated with muscle involvement, high severity score and female gender.(68) MRI is useful for diagnosis and for

delineation of VM.(53) Doppler scan shows slow flow velocity in VM and differentiate from vascular tumour.(69)

Glomuvenous malformations: Glomuvenous malformation is a variant of venous malformation and has different clinical features and histological findings when compared to typical VM.(21) Loss-of-function mutations in 'glomulin'(VMGLOM) gene on chromosome 1p21-22 are found in glomuvenous malformations.(70) They may be autosomal dominant. Glomuvenous malformations present as blue-purple nodules, plaques with pebbly surface, painful and less compressible. They do not extend into deeper structures.(71)

Lymphatic malformations (LM): Lymphatic malformations are composed of abnormally dilated vessels lined by endothelial cells of lymphatic phenotype.(3) Majority of LM (65% -75%) present at birth and rest of them present mostly by 2 years of age.(72) They have equal sex incidence. In a study done by Alqahtani et al, on 186 patients of lymphatic malformations, they found that the lesions were distributed in head and neck(48%), thorax and extremities(42%), internal viscera(10%).(73) According to ISSVA classification, subtypes of LM are cystic (microcystic, macrocystic, mixed), generaized lymphatic anomaly, LM in Gorham-Stout disease and primary lymphedema.(5) There is no uniformity in literature regarding the size of cyst for the division of microcystic or macrocystic LM.(1) Primary lymphedema is a diffuse LM occurs due to dysgenesis of lymphatic network. The subtypes of primary lymphedema and the mutations that causes primary lymphedema are now elucidated.(5) [(Annexure-

I(A)] Macrocystic LM appears as benign swelling with soft and spongy consistency.(49) They occur mostly over neck and axilla. Hence obstruction during vaginal delivery is one of its complications.(74) Other complications include dysphagia, dyspnea, dysphonia, infection and skeletal hypertrophy. Skeletal hypertrophy could be due to local pressure effect or intraosseous LM.(74) Ocular complications include blepharoptosis, proptosis, strabismus, astigmatism and amblyopia.(75)

Microcystic LM (lymphangioma circumscriptum) appears as grouped thin-walled vesicles or hyperkeratotic papules. Their common sites are proximal limbs, axilla and trunk. Most common complication of microcystic LM is lymphorrhoea.(21) Others include infection, bleeding , ulceration. Intralesional hemorrhage can lead to sudden enlargement of LM and is also a predisposing factor for infection.(76) Cellulitis is more common particularly with LM occurring over the head & neck and perineum.(76) There is a report of even squamous cell carcinoma occurring in long standing lymphangioma circumscriptum.(77) Limb hypertrophy is associated with ipsilateral LM. In a study from US on 170 children with lower limb enlargement, 19.6% patients were found to have pure lymphatic malformations.(78)

Generalised lymphatic anomaly, a subtype of LM is composed of multifocal LM affecting skin, subcutaneous tissue, viscera and bone which typically spares cortical boundaries of bone.(1) Gorham-Stout disease, also known as vanishing bone disease, typically composed of lymphatic malformation affecting cortical boundaries of bone

leading to osteolysis.(1,79) Patients with Gorham-Stout disease also have LM affecting skin and viscera.(79)

Diagnosis: Histopathological examination of lymphatic malformation shows multiple dilated thin walled vessels lined by lymphoendothelial cells.(80) D2-40, a novel antibody is very specific immunohistochemical marker for the endothelial cells of lymphatic phenotype.(81) Prenatal ultrasound detects macrocystic LM, like cystic hygromas.(82) Ultrasound examination differentiates macrocystic and microcystic LM.(83) Doppler scan differentiates LM from other vascular malformations. Doppler US shows variable cysts with no flow except in the septa.(18)MRI is the most useful investigation to delineate LM and also to assess the deeper structure involvement.(84) MRI with gadolinium contrast helps in differentiating LM from VM as it shows no enhancement in LM except in septa.(18)

Arteriovenous malformations (AVM)

Clinical profile: Arteriovenous malformations are fast flow vascular malformation that result in shunt between arterial and venous compartment in the absence of capillary bed.(21) AVMs are common among patients between 20 to 40 years of age.(49) They have no sex predilection. AVM presents as ill defined pink mass with raised local temperature and dilated veins. It produces thrill on palpation and murmur on auscultation.(52) AVM can present at any site but most are found in head and neck region.(85) AVM that occurs in lower limbs may produce Kaposi sarcoma like skin changes, known as Stewart-Bluefarb syndrome.(86) In a study done by Enjolras et al on

200 AVM patients, puberty was noticed as trigger in 64 cases, trauma in 39 cases and pregnancy in 25 cases.(87) Complications of AVM, as other vascular malformations depend on the location of malformation. Apart from these, other complications include bone overgrowth, ulceration, arterial steal phenomenon, cutaneous ischaemia, bleeding and high cardiac output failure.(88)

Diagnosis: Ultrasound and Doppler scans are useful screening tools to assess the flow characteristics of the lesion. MRI, magnetic resonance angiogram are non-invasive investigative modalities that delineate the extent of AVM. Angiography is useful as pre-therapeutic investigation and also to guide intra-arterial embolization.(53)

Vascular malformations with other anomalies

Sturge Weber syndrome: It is a rare sporadic disorder with capillary malformation of dermis, leptomeninges and eye. It is described as classical triad of facial dermal capillary malformation, leptomeningeal angiomatosis and vascular malformation of choroidal plexus of eye. Partial forms of the disorder may also be present. Port-wine stain involving first branch of trigeminal nerve is the risk factor of Sturge weber syndrome. Patients with bilateral facial PWS, PWS of eye lids and unilateral PWS involving all 3 trigeminal nerve branches should be screened for ocular and CNS involvement.(55,89) Gingival hypertrophy and accentuation of eruption of teeth were found in case of mucosal involvement of PWS.(90, 91)

Extracutaneous features: Seizures are the most common extra cutaneous feature of SWS.(92) Seizures in SWS initially starts as focal and then become generalized.(93) Almost all these patients with seizures were associated with PWS in V1 alone or V1and V2 dermatomes.(94) The risk factors of developmental delay and mental retardation are bilateral PWS, refractory seizures and extensive neurological involvement.(93–95) Hemiplegia and headache are less commonly reported neurological features. Glaucoma is the most common ocular manifestation of SWS.(92) It occurs during infancy in 60% of patients. Patients with facial cutaneous capillary malformation involving eyelids are more prone to the development of glaucoma.(92)

Diagnosis: MRI is the method of choice for the diagnosis of SWS.(96) MRI with gadolinium enhancement is useful for the detection of leptomeningeal and choroidal plexus vascular malformations and also for the demonstration of parenchymal (gray and white matter) disturbances.(97,98) CT scan is superior to MRI in demonstration of intracranial calcifications and are demonstrated earlier in course compared to plain X-rays.(98) Plain X-rays demonstrate tram-line calcifications in patients more than 2 years of age.(96)

Klippel-Trenaunay syndrome (KTS): It is a sporadic disorder with combination of capillary malformation of an extremity, ipsilateral varicosities/venous malformation, ipsilateral soft tissue and/or bone hypertrophy with or without lymphatic malformation. It was first described by Klippel and Trenaunay in 1900.

Cutaneous features: Capillary malformation in KTS involves almost whole extremity, sometimes extends on to ipsilateral trunk. It typically presents at birth and manifests as port-wine stain which can be in diffuse, patchy or geographic patterns.(96) Geographic pattern of PWS is associated with lymphatic malformations and other complications.(99) KTS commonly involves lower limb when compared to upper limb. Varicose veins may be noted at infancy but becomes prominent in adolescence or late childhood. Varicose vein may involve the whole lateral limb which is thought to be due to persistence of lateral marginal vein/ embryonic vein.(100) Complications associated with venous malformations in KTS are pain, thrombophlebitis, deep vein thrombosis, pulmonary embolism, stasis dermatitis, cellulitis, coagulopathy, rectal bleeding and hematuria.(96,101,102)

Extra cutaneous features: Limb hypertrophy can be due to soft tissue and/or bone hypertrophy.(96)

Diagnosis: There is no uniform consensus on the diagnostic criteria of KTS.(103) According to ISSVA, KTS is diagnosed by the combination of capillary, venous malformation and hypertrophy of one or more extremities with or without lymphatic malformation.(5) Colour doppler scan is done to assess varicose veins and slow flow malformations which is also accurate and reliable non-invasive modality of investigation.(104) X-rays (scanograms) are used to assess bone hypertrophy. MRI is done not only for diagnosis of KTS but also to assess the extent of involvement of venous/ lymphatic malformations, soft tissue and bone hypertrophy.(105)

Phacomatosis pigmentovascularis (PPV): It denotes a group of disorders with the combination of pigmented nevus and capillary malformation. It is considered to be the result of "twin spotting" phenomenon or didymosis.(106) There are 2 classifications of PPV, one by Hasegawa and Yasuhara (1985)(107) and a more recent classification by Happle (2005). **[Annexure I(C)**] PPV is a rare sporadic disorder with slight female predominance. PPV type 2 is the most common type and accounts for about 80% of all reported cases.(108) Capillary malformation of PPV can be segmental or can involve large areas of body.

Diagnosis: The diagnosis of PPV depends mostly on clinical findings. Associated syndromes like SWS, KTS can be detected by appropriate imaging based on location of vascular nevus.(96)

Blue rubber bleb nevus syndrome: It is also known as Bean syndrome and is a rare sporadic disorder with venous malformations of skin and gastrointestinal tract.(96) Cutaneous: The characteristic lesion of this syndrome is blue compressible subcutaneous nodule. Bean referred this lesion after compression as "rubber nipple". Venous malformations can occur at any site of skin, but located usually over trunk and extremities including palms and soles. Few lesions may have pain and tenderness. It can affect ambulation when located over soles.

Extracutaneous: Venous malformations can occur any site of gastrointestinal tract with most common sites being small intestine and colon.(109,110) Common complications

include gastrointestinal bleeding, anemia, intussusception and consumptive coagulopathy.(111)

Diagnosis: Blue rubber bleb nevus syndrome should be suspected in a patient presenting with multiple cutaneous venous malformations and gastrointestinal bleeding. MRI and CT scans help to locate and delineate visceral lesions.(112) Scopies should be done for evaluation of gastrointestinal bleeding.

Maffuci syndrome: It was first described by in 1881 by Angelo Maffuci. It is a sporadic disorder with combination of venous malformations and enchondromas with or without spindle cell hemangioendothelioma.(5)

Clinical features: Venous malformations usually arise over distal extremities.(113) Oral and intraabdominal slow-flow malformations may be found. Sometimes spindle cell hemangioendothelioma presents as cutaneous mass beside venous malformation.(114) Enchondromas present as hard nodules over phalanges and long bones. Complications include phleboliths, short stature, bony deformities/irregularities and chondrosarcomas.(114) It is associated with increased risk of malignancy.

Diagnosis: Plain X rays are done to detect phleboliths and enchondromas. MRI is best tool for evaluation of both vascular lesions and enchondromas.(113)

Parkes Weber syndrome: It is a rare syndrome defined by limb hypertrophy along with red stain (capillary malformation), arteriovenous malformation and arteriovenous fistulas.(5) The most common site is lower limb. Arteriovenous fistulas develop around puberty or following trauma or surgical procedure involving affected extremity. RASA 1 mutation is found to be associated with Parkes Weber syndrome.(115) Complications of Parkes Weber syndrome are high output cardiac failure, bone deformities and abnormal bleeding.(96) Recurrent infections and oozing are the complications if the syndrome is associated with lymphatic malformation. Plain X-rays, duplex scan and MRI scans are useful in the diagnosis of Parkes Weber syndrome and also to delineate the vascular malformations prior to treatment.

Capillary malformation- arteriovenous malformation syndrome (**CM-AVM syndrome):** Capillary malformation- arteriovenous malformation syndrome is a newly described entity with cutaneous capillary malformation and underlying AVM / AVF. RASA 1 gene mutations are found in these patients.(115,116) This gene encodes for protein that determines various growth factors, proliferation and migration of cells including vascular endothelial cells.(117) Capillary malformations in this condition are often small, round with peripheral halo.(116)

PIK3CA-Related Overgrowth Spectrum (PROS):

PIK3CA-related overgrowth spectrum (PROS) is the umbrella term used to encompass all the phenotypic variants with overgrowth caused by somatic PIK3CA mutations.(118) It includes congenital lipomatous overgrowth, vascular malformations, epidermal nevi, spinal/skeletal anomalies/scoliosis (CLOVES) , hemihyperplasia multiple lipomatosis (HHML), facial infiltrating lipomatosis, megalencephaly-capillary malformatiom (M-CM), fibroadipose overgrowth or hyperplasia (FAO), macrodactyly and muscle hemihypertrophy, skin disorders like epidermal nevi, seborrhoeic keratosis and benign lichenoid keratosis.(119) There is still an ambiguity whether KTS comes under the group PROS, as PIK3CA mutations have been detected in few KTS like phenotypes.(131) In the recent workshop conducted in National Institutes of Health (NIH), consensus document regarding clinical diagnostic criteria of PROS was developed [**Annexure-I(D)**].

MATERIALS AND METHODS

Setting:

The study was conducted in the Department of Dermatology, Venereology and Leprosy, Christian Medical College and Hospital. Patients with cutaneous vascular anomalies who presented to Dermatology OPD and patients referred mainly from pediatric surgery, plastic surgery and vascular surgery departments were included in the study.

Study design:

A hospital based cross-sectional study was conducted where in patients fulfilling the inclusion criteria were recruited into the study.

Study duration:

The study was conducted from September 2014 – July 2016 (23 months)

Inclusion criteria:

1**.** Patients with vascular tumours, malformations and overgrowth syndromes diagnosed by clinical features.

2. Patients consenting for the study.

Exclusion criteria:

1. Patients not willing to participate in the study.

2. Patients with acquired vascular tumours like pyogenic granuloma, angiosarcoma.

METHODS

All the patients who were diagnosed to have cutaneous vascular anomalies and fulfilling the inclusion criteria were enrolled into the study. All the subjects and the parents/legal guardian of the subjects were informed about the purpose of the study [**Annexure II**] and informed consent was obtained [**Annexure III**].

All the patients were examined by the principal investigator and relevant details obtained from the patient or parent/legal guardian were entered in a pro forma/clinical research form [**Annexure IV**]. The collected details were entered in an electronic database. Epidata (version 3.1), a data management software was used for the data entry and evaluation.

Demographic details:

Socio-demographic data including patient's age at recruitment into the study, gender, address, duration of symptoms and age of onset were recorded. Age of onset was defined as the age at which patient or parents/legal guardian first noticed the skin lesions.

History pertaining to the disease:

1. Presenting cutaneous complaints (including type of skin lesions, site, size and colour of lesions at onset and of present lesions) and duration of the same were recorded
2. Details of maternal antenatal & perinatal history, mode of delivery, birth weight, course of lesions, exacerbating factors and complications were recorded
3. Associated extracutaneous symptoms (especially related to CNS, CVS, ophthalmic and spine) were also recorded.

Clinical Examination:

Each patient was examined by the primary investigator and the findings were confirmed by the guide. Morphology of skin lesions, site of involvement and the extent of involvement were recorded. Other cutaneous lesions/ birth marks were also recorded. Details of dysmorphic features, extracutaneous abnormalities (especially CNS, CVS, eye, skeletal) were recorded.

The diagnosis of cutaneous vascular anomalies was mostly based on clinical examination and was in accordance with ISSVA 2014 classification of vascular anomalies [**Annexure I (A)**]. Imaging studies were done to characterize the lesion in case of ambiguity and also to delineate the extent of lesion. Patients with PHACES syndrome were diagnosed based on consensus statement for diagnostic criteria of PHACE syndrome [**Annexure I (B)**]

Klippel-Trenaunay syndrome was diagnosed based on clinical and radiological findings. It is the combination of capillary malformation of an extremity, ipsilateral varicosities/venous malformation, ipsilateral soft tissue and/or bone hypertrophy with or without lymphatic malformation.

Patients with PROS were diagnosed based on the clinical diagnostic criteria of PROS that were described in the consensus document [**Annexure I (D)**].

Investigations

Imaging studies

Radiological investigations were done wherever necessary depending on anatomical location (if adjacent to vital structures) and nature of lesion to determine cutaneous and extracutaneous features of vascular anomalies and their complications.

X ray skull and magnetic resonance imaging of brain were done in cases of facial capillary malformations. Ultrasonography with doppler study of affected area was done to characterize vascular anomaly. Magnetic resonance imaging of affected area was done to delineate the extent of the lesion if adjacent to vital structures. Ultrasonography of abdomen was done in cases of multiple hemangiomas to look for hepatic hemangiomas.

Laboratory investigations:

Relevant laboratory investigations based on nature of the vascular anomaly included hemoglobin, platelets, D-dimer and thyroid function tests. D-dimer levels were done predominantly in cases of suspected venous malformations. Platelet count and D-dimer levels were done to diagnose Kasabach-Merritt phenomenon. Thyroid function tests were done in cases of multiple hemangiomas and suspected visceral hemangiomas.

Skin biopsy:

Skin biopsy was done to confirm the diagnosis in cases of tufted angioma, KHE and microcystic lymphatic malformations along with few cases of capillary malformation. Immunohistochemistry was done with lymphatic markers (D2-40) in few doubtful cases to confirm the diagnosis of lymphatic malformation.

Sample size:

In a pilot study done by the primary investigator, 14 cases of cutaneous vascular anomalies were found in a period of 4 months.

Based on the pilot study:

Number of cases found in a period of 4 months – 14

Duration of present study period- Sep 2014 to July 2016 = 23 months

Number of cases expected to be found in study period - 14 x 23/4 = 81

However, as it is a descriptive study all the consecutive consenting patients with a diagnosis of cutaneous vascular anomalies during the study period between September 2014 – July 2016 attending Dermatology unit I out-patient department and referred from other departments were recruited in the study.

Statistical analysis

All numerical variables were described using mean and standard deviation. Categorical variables were summarized using frequencies and percentages. *P* value was calculated using Fisher's exact test and Kruskal-Wallis equality-of-populations rank test wherever applicable.

Funding:

The study was funded by the Fluid research grant of CMCH, Vellore.

Study approval

The study was approved by Institutional Review Board (Research and Ethics committee) [IRB no 9082].

RESULTS

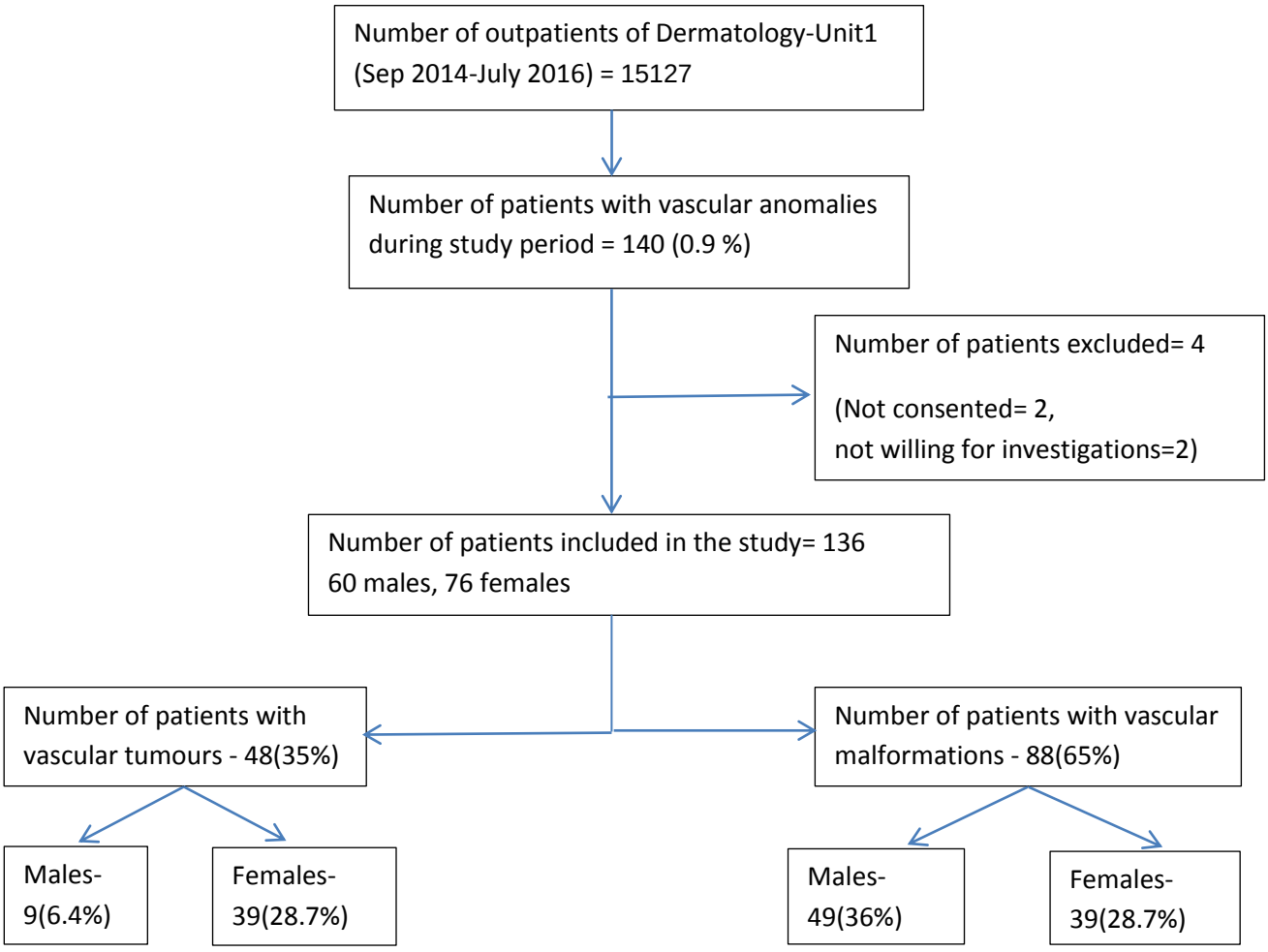


Figure 1: Demographic profile of vascular anomalies

Demographic profile

Out of a total of 15127 new patients seen during the period of study, 0.89% (n= 136) patients with the diagnosis of vascular anomalies and related syndromes were included in the study between September 2014 to July 2016 (23 months). [**Figure 1]**

Geographical location

Geographical distribution of the patients was as follows: 63 (46.3%) were from north India, 60 (44.1%) were from south India and 13 (9.6%) were from Bangladesh.

Age distribution

Age at presentation: The mean, standard deviation and median of age of the patients at presentation were 11.96 ± 16.61 years and 5 years respectively (range 1 month- 73 years). Majority patients (99, 72.8%) belonged to pediatric age group (age ≤ 18 years).

Age of onset: Sixty five patients (47.8%) had the onset of vascular anomalies at birth. Mean age of onset of the lesions was 30.6 ± 103 months.

Gender distribution

Among 136 patients of vascular anomalies, 60 (44%) patients were male and 76 (56%) patients were female with male to female ratio of 1: 1.27. [**Figure 2]**

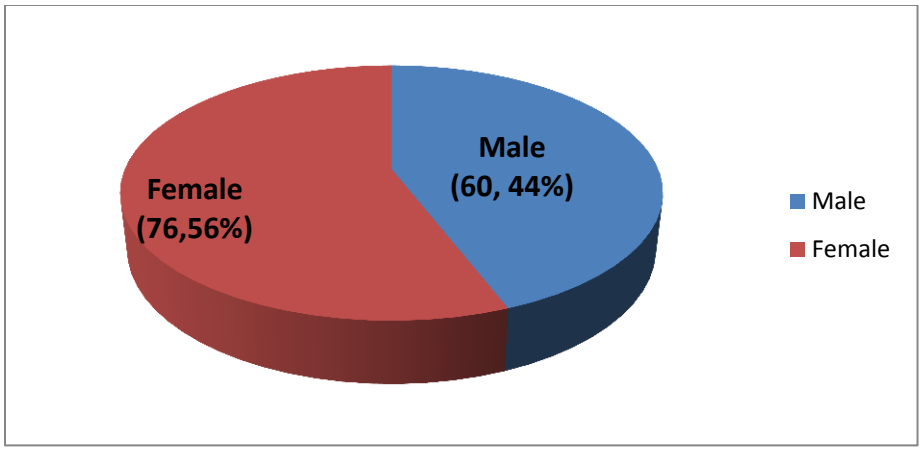


Figure 2: Gender distribution of vascular anomalies

Maternal antenatal & perinatal history: All the patients with vascular anomalies had uneventful maternal, antenatal and perinatal history.

Subtypes of vascular anomalies: Among 136 patients of vascular anomalies, 48 (35%) had vascular tumours and 88 (65%) had vascular malformations. [**Figure 3]**

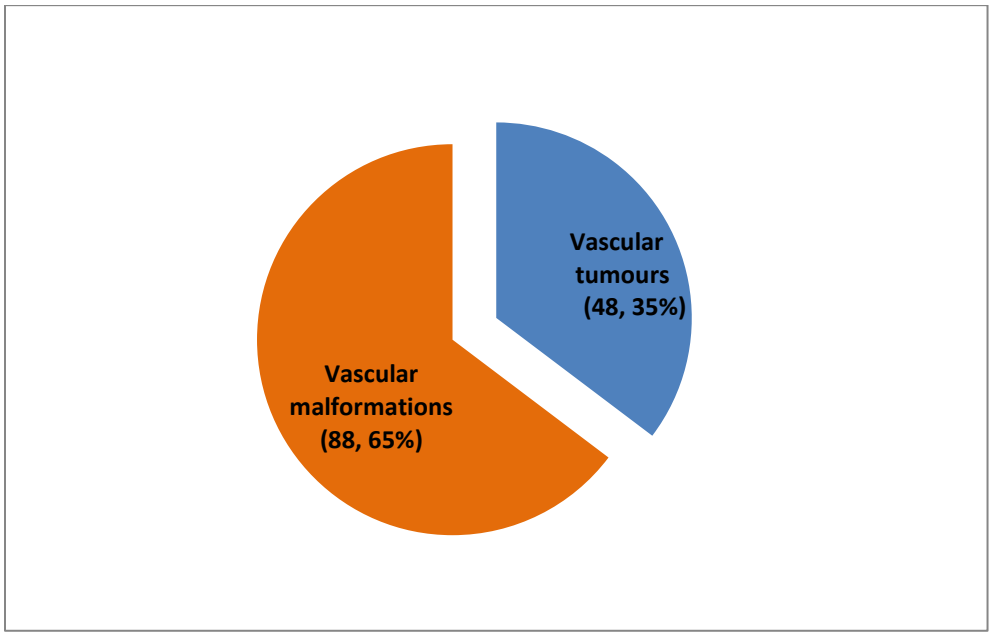


Figure 3: Relative frequency of vascular anomalies

Vascular tumours

48 patients (39 F, 9 M) out of 136 patients had vascular tumours. Female predominance was noted in all types of vascular tumours [**Figure 4**]. IH (n=42, 88%) was the commonest subtype. Other types were CH (n=4, 8%), TA (n=1, 2%) and KHE (n=1, 2%). Among CH, 3 were RICH and 1 patient had NICH.

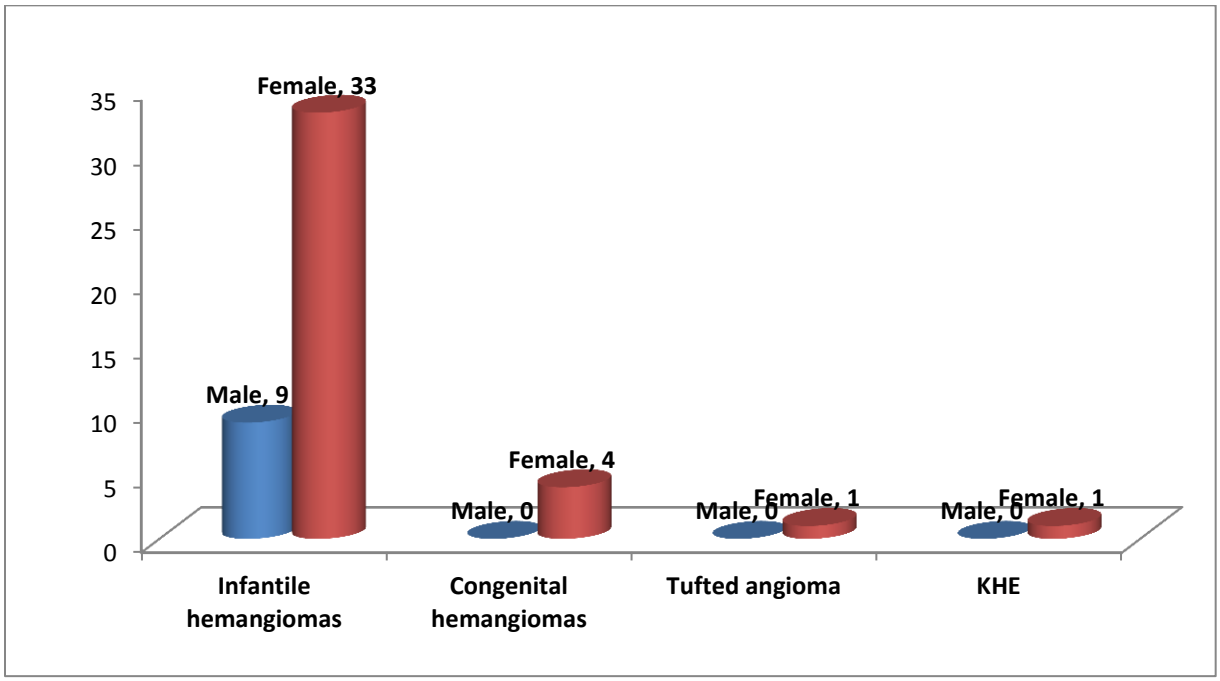


Figure 4 - Gender distribution in vascular tumours

Age of onset of disease and age at presentation

The mean age of onset of vascular tumours was 0.55 months with the range from 0 to 6 months of age.

The mean age of patients presented with vascular tumours was 1.15± 2.4 years. All the patients with vascular tumours belonged to pediatric age group.

Table 1: Comparative clinical profile of each subtype of vascular tumours

Vascular tumours	Anatomical distribution (n,%)	Complications (n,%)	Extra cutaneous involvement (n,%)
IH	Head & neck-32(76%) Trunk- 9(21.4%) Upper limbs- 6 (14.3%) Lower limbs- 2 (4.8%) Genitalia- 1(2.4%)	Ulceration-7(16.7%) Bleeding-6(14.3%) Infection- 3(7.14%) Visual obstruction-1(2.4%) Airway obstruction-1(2.4%) Facial disfigurement-2(4.8%)	CNS- 2(4.8%) Ocular – 2(4.8%)
RICH	Upper limb-1 Lower limb-1 Buttocks-1	-	-
NICH	Head & neck, shoulder, chest-1patient	-	-
TA	Abdominal wall	Elevated D-dimer levels	-
KHE	Right knee	Kasabach-Meritt syndrome	-

Infantile hemangiomas

Frequency, gender and age distribution (demographic profile)

IH was the most common cutaneous vascular tumour and accounted for 88% patients with vascular tumours (n=42). It was more common in females (M/F ratio- 1: 3.67). Majority patients (30, 71.4%) with IH presented within first year of their life. The mean age of patients who presented with IH was 1.09 ± 2.27 years.

Age of onset [**Table 2**]

Most cases of IH were noticed in the first month of life and accounted for 35 patients. Initial/ precursor lesions were noted at birth in five patients. None of the patients had onset of IH after 6 months of age. The mean age of onset of IH was 0.59 months (approximately 16 days)

Table 2: Age of onset of IH

Age of onset	**No. of patients with IH**
0- 1month	35
1 – 6 months	7
>6 months	0

Anatomical distribution of IH [Figure 5]

All the IH presented as red plaques (n=41) except for one case of neonatal hemangiomatosis that presented as multiple red papules. Most of IH involved head and neck region accounting for 76% patients (n=32). Trunk was the second most common site of involvement of IH accounting for 21.4% patients (n=9). It included patients with IH over the chest (n=4, 9.5%), back (n=4, 9.5%) and abdomen (n=1, 2.4%). The limbs were involved in 19% patients (n=8); upper limbs in 14.3% patients (n=6) & lower limbs in 4.8% patients (n=2). The other anatomical site of involvement was genitalia (n=1, 2.4%). Majority of patients had single hemangiomas accounting for 36 patients (85.7%). Six patients (14.3%) had multiple lesions. One patient had multiple disseminated red papules while in the rest of the cases the average number of hemangiomas per patient was 4.

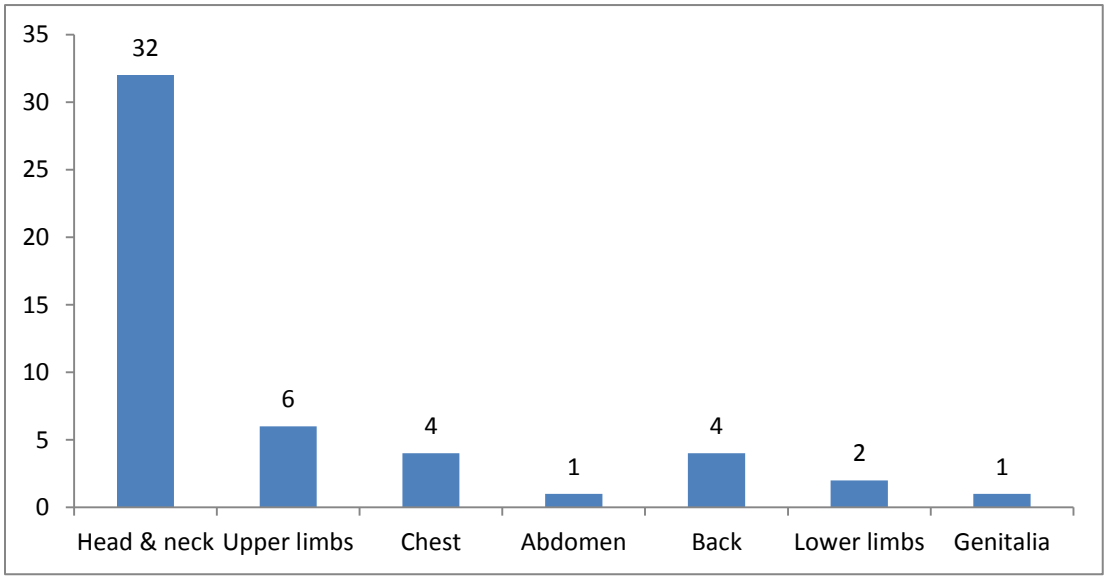


Figure 5: Anatomical distribution of IH

Complications of IH [Figure 6]

Complications were found in 11 patients (26.2%) with IH. Ulceration was the most common complication, presented in 7 patients (16.7%). Bleeding following trivial trauma was the second most common complication that presented in 6 patients (14.3%). Three IH (7.14%) were complicated with infection. One patient had visual field and airway obstruction. Both children (4.8%) with PHACES syndrome had disfigurement of face due to large facial hemangiomas. One among them had nasal septal resorption leading to facial disfigurement without airway obstruction.

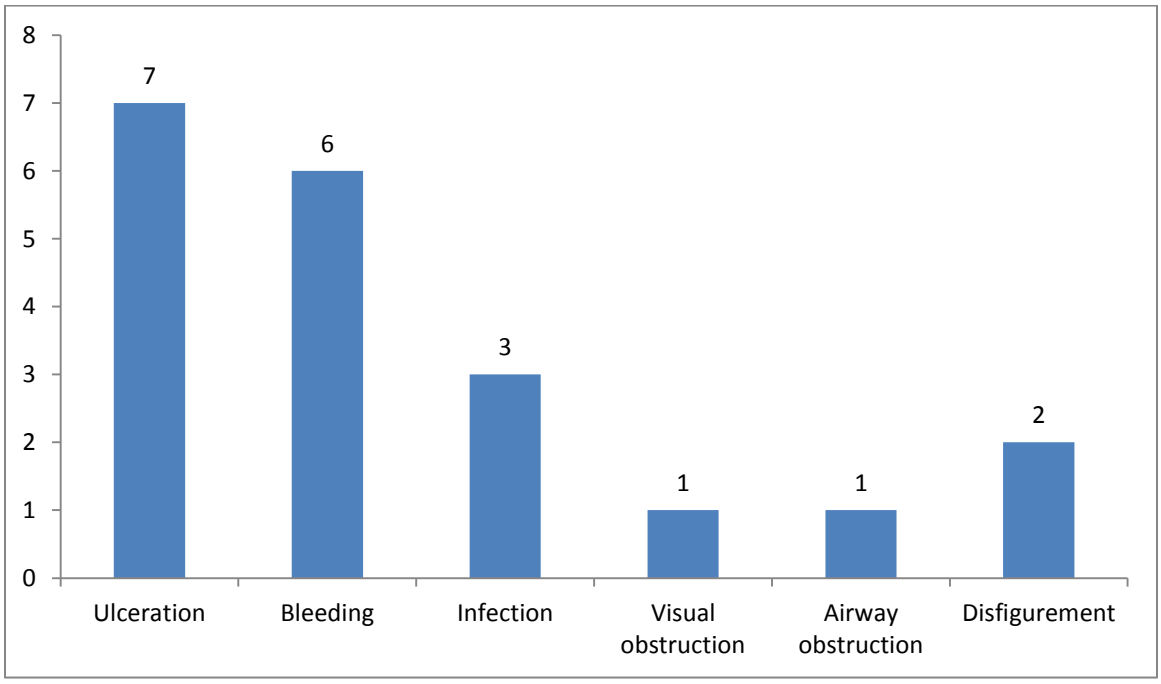


Figure 6: Complications of IH

Preterm delivery and birth weight: Majority of patients with IH were born at full term gestation. Six children (14.3%) with IH were preterm babies with low birth weight. Among them, three children had very low birth weight (< 1500 gms) with the lowest being 1.16 kg at birth.

Mucosal involvement: Mucosal lesions were present among 9 patients (21.4%) with IH. Seven patients had involvement of oral mucosa. Two patients each had involvement of conjunctival and nasal mucosa. One patient had nasopharyngeal and laryngeal involvement.

Imaging studies: Ultrasound abdomen done in 3 patients with multiple hemangiomas did not show systemic involvement. Doppler was done in 4 patients with infantile hemangiomas which showed internal vascularity with arterial and venous flow.

Syndromes associated with IH

Features of patients with PHACES syndrome:

Patient 1

-Large involuting facial hemangioma (> 5cm) with nasal septal resorption

- Right eye squint.

- MRI brain showed Dandy-walker malformation (posterior fossa structural anomaly) and cerebellar artery hypoplasia.

- Echocardiography was normal

Patient 2

- Large facial hemangioma (> 5cm) extending to involve right masticator space, parapharyngeal space, submandibular region, parotid gland , right orbit, right cavernous space

- Visual field obstruction

- MRI brain showed cerebellar hypoplasia (posterior fossa structural anomaly) & cerebellar artery hypoplasia

- Echocardiography was normal

Congenital hemangiomas

Frequency, gender and age distribution (demographic profile)

Four patients accounting for 8% of vascular tumour cases had CH. Of these, 3 patients had RICH and one patient had NICH. All four patients were girls and their age ranged from 3 months to 8 years.

Anatomical distribution: The girl with NICH had large dull red plaque over right side of occiput, neck, right shoulder and right side of upper chest. The sites of involvement among patients with RICH were right upper limb, right lower limb and buttocks respectively.

Complications: None of the patients with CH had experienced complications.

Preterm delivery and birth weight: All patients with CH were born at full term. One patient with RICH had low birth weight (2.2 kg). The others were born with birth weight of above 2.5kg.

Extracutaneous features: There was no significant extracutaneous involvement among CH except for soft tissue involvement of occiput, neck, chest in the patient with NICH.

Imaging studies: MRI and US were done in the patient with NICH which showed soft tissue swelling/ enhancement with minimal cystic vascular spaces. US alone was done in a patient with RICH in which it was normal

Tufted angioma

Clinical profile: One patient, a 1 year old female child had brownish indurated plaque of size 4 cm x 3.5 cm over left side of abdomen. It was noted at the age of 2 months. She was full term baby with low birth weight (2.3 kg). She had no significant maternal antenatal history, exacerbating factors, complications or extracutaneous features.

Skin biopsy: Skin biopsy showed skin tufts of proliferated capillaries lined by plump endothelial cells separated by normal dermal collagen and were seen dispersed in the superficial and predominantly in the middle and deep dermis. Occasional blood vessels showed fibrin thrombi.

Lab parameters: She had high D-dimer levels (1035 ng/ml) [normal < 250ng/ml]. All the other parameters including hemoglobin, platelets and TSH were within normal limits.

Imaging studies: Ultrasound examination of the lesion showed soft tissue thickening with internal vascularity.

Kaposiform hemangioendothelioma

Clinical profile: A 4 month old girl, born full term with low birth weight (2.39 kg) presented with dusky red indurated plaque of size 5cm x4 cm over right knee. It was noted at the age of one month. Increased local temperature was found on palpation of the lesion. She had Kasabach-Meritt phenomenon. She had no significant exacerbating factors or extracutaneous features. Biopsy was not done to confirm the diagnosis.

Imaging studies: Doppler US and MRI of the lesion showed solid tissue mass with arterial flow and no cystic spaces. MRI also showed post contrast enhancement of the lesion.

Lab parameters: The girl was found to have high D-dimer levels (2810 ng/ml) and low platelets (38000 /ml) which was part of Kasabach-Meritt syndrome. Other parameters were normal.

Table 3: Summary of imaging studies in vascular tumours

Vascular tumour	Doppler US		MRI imaging		Role/ relevance
	Number	**Findings**	**Number**	**Findings**	
IH (n=42)	4(Doppler)	Solid mass along with arterial and venous waveforms	2 (MRI brain)	Posterior fossa structural abnormalities and cerebellar artery hypoplasia	Diagnostic & to look for associations
RICH (n=3)	1	Solid tissue over skin and subcutis with no deep involvement	-		Extent of lesion
NICH (n=1)	1	Soft tissue enhancement with internal vascularity	1	Soft tissue enhancement with cystic vascular spaces	Diagnostic & Extent of lesion
TA (n=1)	1	Soft tissue thickening with internal vascularity	-		Diagnostic
KHE (n=1)	1	Soft tissue mass with arterial flow	1	Post contrast enhancement of the lesion	Diagnostic & extent of lesion

Vascular malformations

Vascular malformations were detected in 88 patients. There were 49 males and 39 females. Male predominance was noted in capillary malformations, LM and AVM. Female predominance was found in simple VM [**Figure 7**] Among malformations, capillary malformation (n=34, 38.6%) was the commonest type. Other types in descending order were isolated LM (n=14, 16%), isolated VM (n=10, 11%), VLM (n=6, 6.8%) and AVM (n=6, 6.8%). Syndromes with vascular malformations were found in 15 patients. Vascular malformation associated syndromes in descending order were KTS (5 patients), SWS (4 patients), PPV (4 patients), CLOVES syndrome (2 patients), BRBB (1 patient), HHT (1 patient).

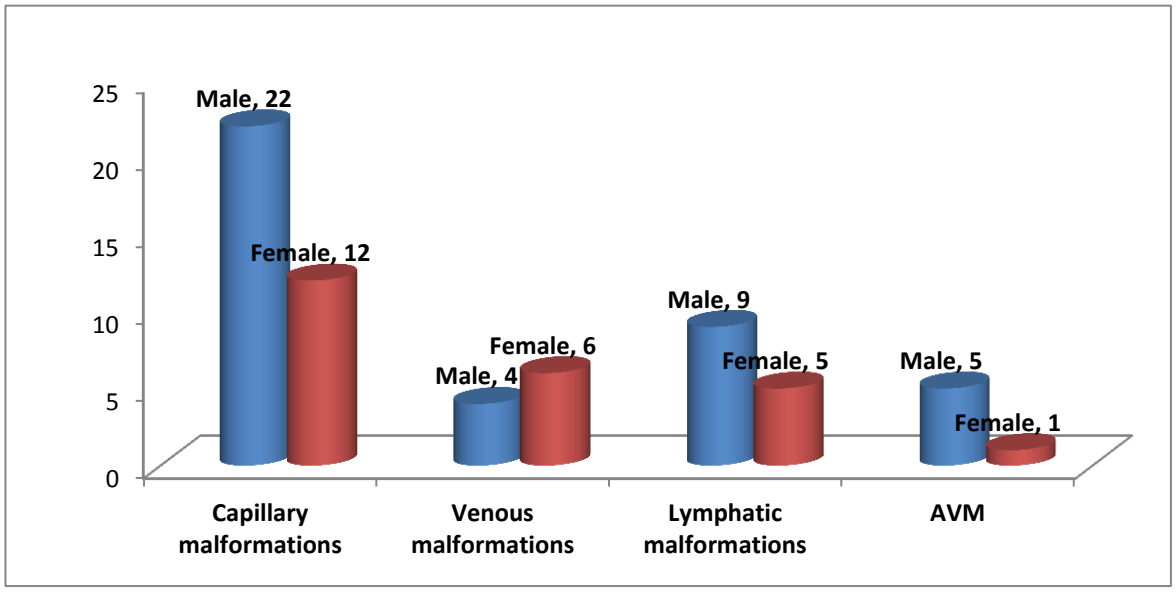


Figure 7: Gender distribution of vascular malformations (non syndromic)

Age of onset of disease and age at presentation

The mean age of onset of vascular malformations was 48.8 ± 127 months (approximately 4 years) with the range from 0 to 72 years.

The mean age of patients presented with vascular malformations was 18.4 ± 18.05 years with the range from 1 month to 73 years.

Capillary malformations (Non syndromic)

Frequency, gender and age distribution (demographic profile)

Capillary malformations were the most common vascular malformations and accounted for 38.6% patients with vascular malformations (n= 34). Among them, 31 patients had port-wine stains and 3 were patients of cutis marmorata telangiectatica congenita. Capillary malformations were more common in males with male to female ratio of 1.83: 1. Mean age at presentation was 24 years.

Age of onset: Majority of the capillary malformations accounting for 25 patients (80.6%) were noted at birth. The mean age of onset of capillary malformations was 12.3 months. Three patients of acquired PWS were detected with the age of onset ranged from 1.5 years to 23 years.

Anatomical distribution [Figure 8]: All the capillary malformations presented as red macular areas (port-wine stains). Most of the capillary malformations involved head & neck region accounting for 46% patients (n=17). Other anatomical sites involved in descending order were upper limbs (n=10, 27%), lower limbs (n=5, 14%), chest (n=2, 6.4%), back (n=2, 6.4%) and genitalia (n=1, 3%).

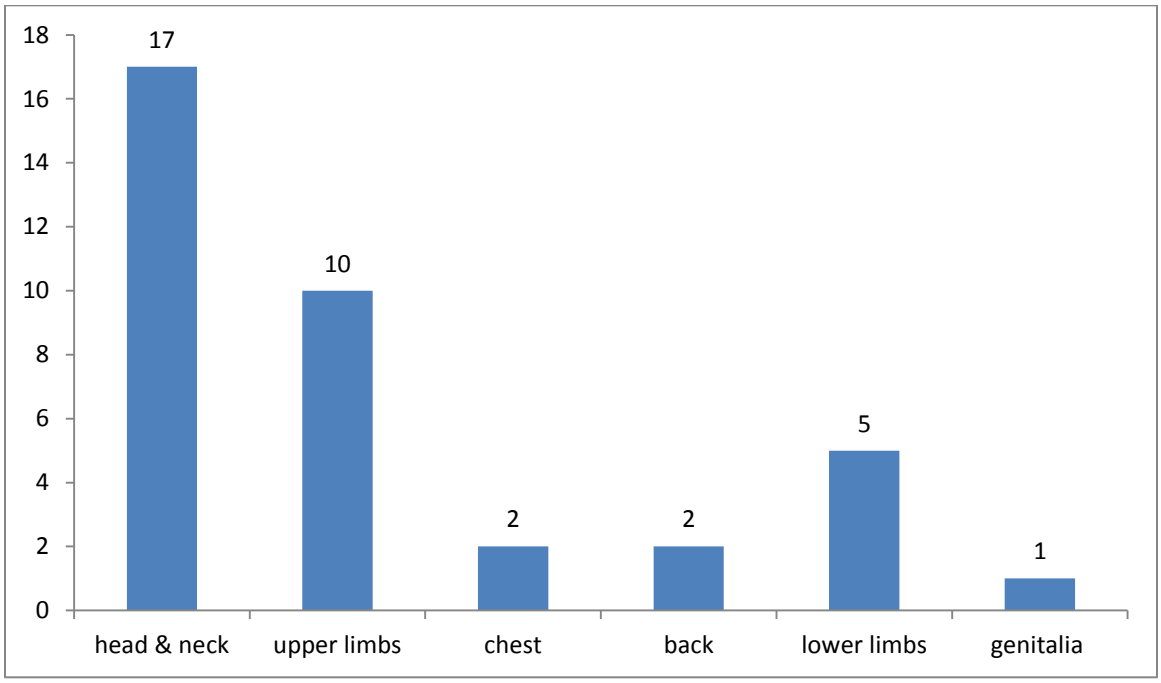


Figure 8: Anatomical distribution of capillary malformations

Complications: One patient with capillary malformation had bleeding following trauma. None of the other patients with capillary malformations had complications.

Preterm delivery and birth weight: Majority patients with capillary malformations were born at full term except for two preterm children (6.4%). Four patients had low birth weight (<2.5 kg). Others were born with birth weight of above 2.5kg.

Exacerbating factors: Two patients with acquired PWS had antecedent trauma and one patient had exacerbation with pregnancy. One patient with congenital PWS had experienced exacerbation at puberty.

Mucosal involvement: Six patients (19.3%) had mucosal involvement. Oral mucosa (lip, buccal mucosa, palate) was involved in 5 patients and conjunctiva was in one patient.

Other cutaneous findings: Other cutaneous findings among the patients with capillary malformations were café-au-lait macule (1 pt), nevus anemicus (1 pt), nevus depigmentosus (1 pt) and giant acrochordon (1 pt).

Extracutaneous features: Abnormal CNS features (developmental delay), abnormal eye findings (orbit involvement), spine abnormalities (scoliosis) were found in 1 patient each. The patient with abnormal CNS findings was a case of Prader Willi syndrome and developmental delay was probably secondary to it. Limb abnormalities include hypertrophy in 3 patients, atrophy and arthrogryposis in one patient each. One patient was found to have hemangiomas of liver.

Imaging studies: Doppler imaging with ultrasound examination was done in 4 patients which showed slow flow pattern with no deeper involvement in 3 patients. Colour doppler of one patient showed involvement of right side of face, right orbit and retromolar area with capillary malformation. X ray skull done in 3 patients was normal.

Venous malformations (Isolated)

Frequency, gender and age distribution (demographic profile)

VMs were found among 11% (n=10) patients with vascular malformations. These were more common in females with male to female ratio of 1: 1.5. Mean age of patients at presentation was 17 years.

Age of onset: One half of the VMs accounting for 5 patients were noted at birth. Mean age of onset of VM was 106.2 months (approximately 8.8 years)

Anatomical distribution [Figure 9]

Majority VMs (n=9, 90%) presented as bluish swellings. Most of the simple/isolated VMs involved upper limbs accounting for 60% patients (n=6). Other anatomical sites involved were lower limbs (n=2, 20%), head & neck region (n=2, 20%). One patient with VM of upper limb had involvement of ipsilateral side of chest.

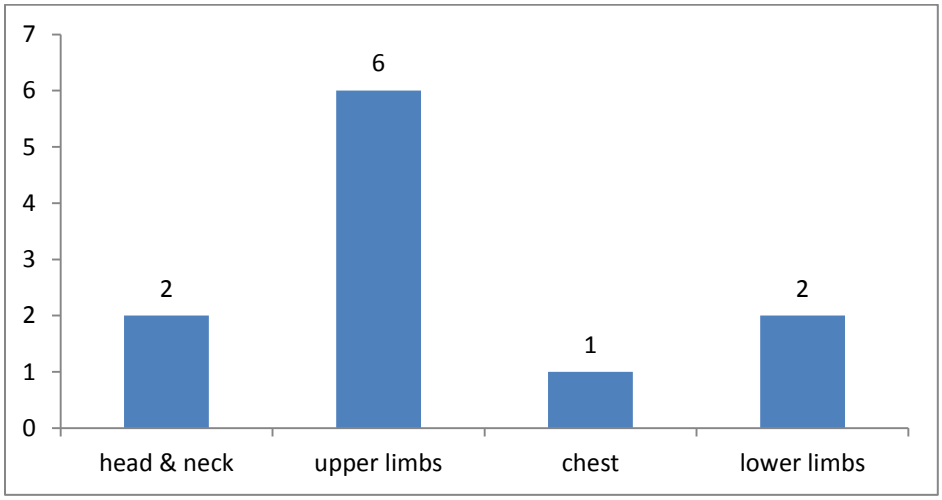


Figure 9: Anatomical distribution of VM

Complications: Four patients with VM had bleeding on trivial trauma. One patient had thrombosis of the VM

Preterm delivery and birth weight: All patients with VM were born at full term and none of them had history of low birth weight.

Exacerbating factors: One patient had experienced exacerbation following trauma. No other exacerbating factors were found among patients with simple VM.

Mucosal involvement: Only one patient had mucosal involvement of VM. It involved lower lip of the patient.

Other cutaneous findings: One patient with isolated VM had pigmentation in Blaschkoid pattern over foot.

Extracutaneous features: Two patients with isolated VM had limb hypertrophy. One patient had intraosseous involvement of VM. No other extracutaneous features were found among patients with simple VM

Lab parameters: D-dimer levels were done in 4 patients with isolated VM which were large and/or symptomatic. Among them, 3 patients had elevated D-dimer levels (> 250 ng/ml) and one patient had highly elevated D-dimer levels of 1174 ng/ml. Other cases had normal values of D-dimer.

Imaging studies: Doppler imaging and MRI scans were done in 4 patients each. Both imaging studies showed slow flow pattern in malformations with venous flow. In one

patient with simple VM, MRI showed intraosseous involvement. Imaging showed phleboliths in the lesions of 2 patients.

Lymphatic malformations (Isolated)

Frequency, gender and age distribution (demographic profile): LMs were found among 16% patients with vascular malformations (n= 14). These were more common in males with male to female ratio of 1.8:1. Mean age at presentation was 15.6 years.

Age of onset: LMs were evident at birth in 4 patients. Mean age at onset of LMs was 107 months (approximately 8.9 years)

Morphology and anatomical distribution [Figure 10]: Majority of LM (n=10, 71.4%) presented as clear vesicles, 3 patients presented as haemorrhagic vesicles and one patient with Milroy's disease presented with bilateral lower limb swelling. Out of 14 patients, two had multiple site involvement whereas single site involvement was seen in 12. Most of the LM involved trunk (chest-3 patients, back-2 patients) accounting for 35.7% patients (n=5). Other anatomical sites involved were lower limbs (n=3, 21.4%), genitalia (n=3, 21.4%), head & neck region (n=2, 14.3%). Upper limb and buttocks were involved by LM in one patient each.

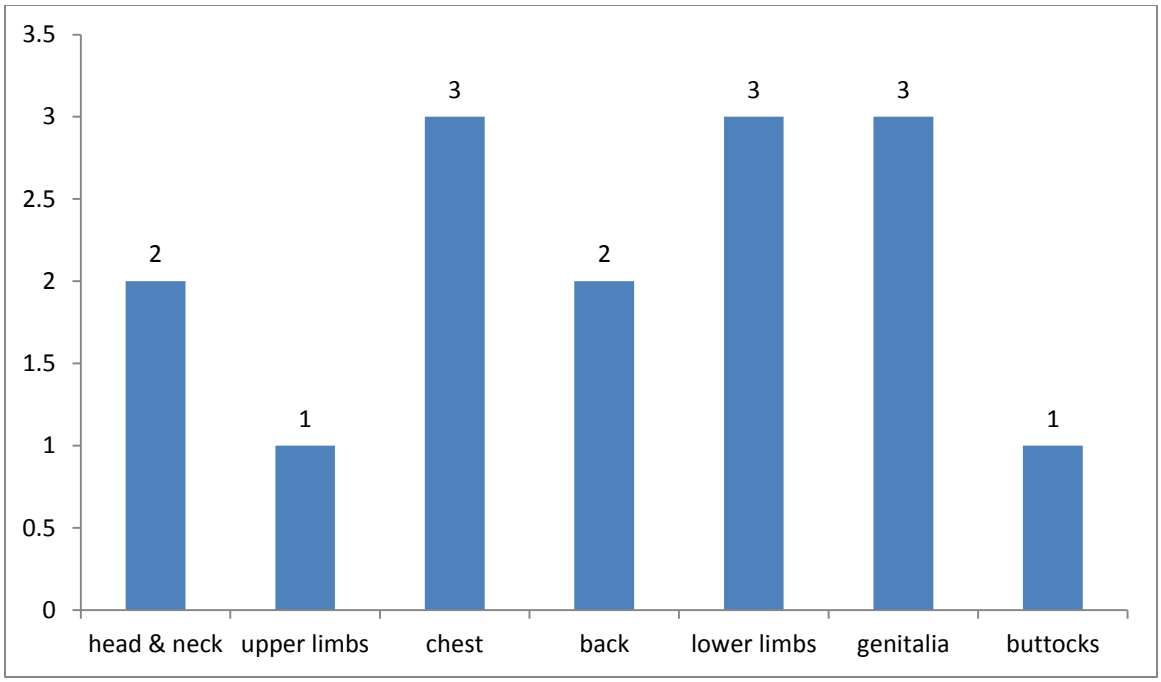


Figure 10: Anatomical distribution of LM

Complications: Five patients with LM had bleeding on trauma. Four patients complicated with oozing. Two patients had infection and one had ulceration of LM.

Preterm delivery and birth weight: One patient with LM had history of preterm delivery and born with very low birth weight of 1.34 kg.

Exacerbating factors: One patient had experienced exacerbation at puberty. No other exacerbating factors were found among patients with LM.

Mucosal involvement: Two patients had mucosal involvement of LM. One patient had involvement of vulva and other had involvement of urethral meatus.

Other cutaneous findings: One patient with isolated LM had nevus depigmentosus.

Extracutaneous features: One patient with LM showed involvement of left parotid gland and submandibular salivary gland with malformation. No other extracutaneous features were found among patients with isolated LM

Lab parameters: D-dimer level was done in 1 patient with LM which presented with subcutaneous swelling of right thigh and exophytic verrucous plaques around right knee. The patient had normal D-dimer level.

Skin biopsy: Skin biopsy was done in 6 patients with isolated LM which showed multiple ectatic lymphatic channels in dermis lined by flattened endothelium containing proteinaceous pale eosinophilic fluid within their lumen. D2-40 stain was done in one patient with LM.

Imaging studies: US/Doppler and MRI scans were done in 4 patients and 6 patients respectively. Both imaging studies showed slow flow pattern with no blood flow in malformations.

Arteriovenous malformations (AVM)

Frequency, gender and age distribution (demographic profile): AVM were found among 6 patients. AVM were more common in males with male to female ratio of 5 : 1. Mean age at presentation was 28 years.

Age of onset: Two patients had the onset of AVM at birth. Mean age at onset of AVM was 132 months (11 years)

Anatomical distribution: Three patients had involvement of head & neck region accounting for 50% patients (n=3). Other anatomical sites involved were abdomen (1 patient), back (1 patient) and upper limb (1 patient) Thrill and bruit present in 4 patients with AVM.

Complications: Two patients with AVM had history of bleeding from the lesion following trauma. Others did not have any complications

Preterm delivery and birth weight: All patients with AVM were born at full term with birth weight of above 2.5kg.

Exacerbating factors: One patient had experienced exacerbation at puberty.

Mucosal involvement: Two patients (33.3%) had mucosal involvement. One patient had lower lip involvement and other had tongue involvement.

Other cutaneous findings: Other cutaneous findings found among patients with AVM were nevus spilus and acrochordon.

Extracutaneous features: None of the patients with AVM had extracutaneous involvement

Imaging studies: Doppler was done in 4 patients whereas MRI was needed in 2 patients. Both imaging studies showed high blood flow pattern in the lesions.

Combined venolymphatic malformations (VLM)

Frequency, gender and age distribution (demographic profile): VLM were found among 6 patients. VLM had no gender predilection with male to female ratio of 1: 1. Mean age at presentation was 12.3 years.

Age of onset: Two patients had the onset of VLM at birth. Mean age at onset of VLM was 48.5 months (approximately 12 years)

Anatomical distribution: Three patients had multiple site involvement. Most of the VLM involved lower limbs accounting for 50% (n=3). Other anatomical sites involved were upper limbs (2 patients), genitalia (2 patients), chest (1 patient), perineum (1 patient) and buttocks (1 patient).

Complications: Four patients with VLM had history of bleeding following trauma. In one patient both bleeding and oozing were present.

Preterm delivery and birth weight: All patients with VLM were born at full term. Among them one born with low birth weight (2.3kg)

Exacerbating factors: No exacerbating factors were found among VLM patients.

Mucosal involvement: Two patients had mucosal involvement (anorectal mucosa)

Extracutaneous features: Two patients had extensive intraabdominal and pelvic VLM. In one patient VLM involved lower abdominal mesentery, sigmoid mesocolon, superior wall of urinary bladder, bilateral ischiorectal fossae and abutted right adrenal gland. In

other patient VLM involved recto-sigmoid region, right parametrium till pelvic side wall. Limb hypertrophy was found in 2 patients with VLM whereas limb atrophy was found in 1 patient.

Lab parameters: One out of 3 patients in whom D-dimer levels were done, had elevated levels. Two patients had anemia with hemoglobin values of 5.8g/dl and 9.2g/dl. Stool examination for occult blood was positive multiple times in these patients. Endoscopy of one patient with intraabdominal VLM showed no active intraluminal source of bleed but noticed extrinsic compression of rectum and sigmoid colon by the abdominal VLM. It also revealed cecal nodules with submucosal hemorrhages and edematous ileal & colonic mucosa. Colonoscopy of the other patient with VLM over rectosigmoid region also showed no active intraluminal source of bleed. It showed prominent submucosal veins, edematous and erythematous mucosa from anal verge to 20 centimeters proximally.

Imaging studies: Colour Doppler was done in 5 patients whereas MRI was needed in 4 patients. Both imaging studies showed low flow void in the lesions. Imaging studies showed the extent of lesions as mentioned above (extracutaneous features of VLM). Lateral marginal vein/embryonic vein was found in one patient.

Vascular malformations with other anomalies

Sturge Weber syndrome (SWS) [Table 3]

Frequency, gender and age distribution (demographic profile): Four patients were diagnosed with SWS. It was found in 2 males and 2 females with equal male to female ratio. Mean age of patients with SWS was 1.53 years

Anatomical distribution: Three patients had large areas of capillary malformations involving the areas supplied by trigeminal branches and other extensive areas of the body. Among them, one patient had PWS over face and CMTC all over the body. One patient had capillary malformation limited to the left V1 and V2 dermatomal areas.

Preterm delivery and birth weight: All patients with SWS were born at full term gestation and with normal birth weight.

Mucosal involvement: Two patients with SWS had mucosal involvement. One patient had capillary malformation over the palate and buccal mucosa. Other patient had melanosis oculi and capillary malformation over the buccal mucosa.

Extracutaneous features: Eye manifestations included glaucoma in 3. CNS involvement manifested as seizures in 3 patients and developmental delay in one patient. Overgrowth was found in two patients with SWS. One patient had macrocephaly along with hypertrophy of left upper and lower limbs. The other patient had overgrowth of right cheek, right arm and right thigh.

Associated features: Three patients with SWS were associated with dermal melanocytosis and were further categorized as PPV type 2b in two patients and the other patient as PPV 5b.

Imaging studies: All the patients with SWS had undergone imaging studies. MRI brain was done in all patients and CT brain was done in one patient. Various features suggestive of SWS were detected, such as leptomeningeal angiomatosis, dilated tortuous vessels, cerebral atrophic changes and gyral calcification.

Table 3: Demographic, clinical and imaging features of SWS

Characteristics	**SWS**
Number of patients	4
Gender	M:F – 1 : 1
Mean age of patients	1.53 years
Age of onset	At birth- 4 pts
Location	Generalised CM including V1, V2 dermatomes – 3 pts Limited to V1, V2 dermatomes- 1 pt
Mucosal involvement	1 pt- CM of palate, buccal mucosa 1 pt- melanosis oculi and CM over buccal mucosa
Complications	Nil
Birth weight	Normal
Extracutaneous features	Glaucoma- 3 pts Seizures- 3 pts Developmental delay- 1 pt Limb overgrowth- 2 pts Macrocephaly- 1 pt
Lab parameters	Normal
Imaging studies	MRI brain- 4 pts CT brain- 1 pt *Results:* Leptomeningeal angiomatosis, dilated tortuous vessels, cerebral atrophic changes and gyral calcification

Phacomatosis pigmentovascularis (PPV) [Table 4]

Frequency, gender and age distribution (demographic profile): Five patients (3F, 2M) with the mean age of 1.38 years (range 1.5yr-9 yrs) were diagnosed with PPV. All presented at birth. The types seen were PPV type 2b with SWS (2 patients), PPV type 2b with KTS(1 patient), PPV type 2a(1 patient) and PPV type 5b(1 patient).

Anatomical distribution: Four patients had disseminated large areas of capillary malformation all over the body including head and neck regions. One patient had capillary malformation limited to the left lower limb.

Mucosal involvement: Three patients with PPV had mucosal involvement.All 3 patients had melanosis oculi. Oral mucosal involvement included capillary malformation of palate and buccal mucosa (1 patient), buccal mucosa alone (1 patient) and mucosal neuroma (1 patient).One patient had dermal melanocytosis of palate.

Extracutaneous features: Glaucoma was found among 4 patients whereas seizures and developmental delay were found in 2 patients and 1 patient respectively. Overgrowth was found in all patients with PPV which were macrocephaly (2 patients), overgrowth of right cheek, right arm and right thigh (1 patient), left upper and lower limb hypertrophy (2 patients) and left lower limb hypertrophy (1 patient)

Associated features: Three patients with PPV were associated with SWS. One patient was associated with KTS of left lower limb and also had other features of

neurofibromatosis type 1. This patient had bilateral Lisch nodules of iris and glaucomatous discs.

Imaging studies: MRI brain was done in 4 patients and Doppler of limb was done in 2 patients. In MRI brain, various features suggestive of SWS (mentioned under imaging studies of SWS) were detected among 3 patients. MRI brain of one patient showed foci of abnormal intensity in basal ganglia and cerebellar white matter, moya moya phenomenon (segmental narrowing of cerebral arteries) which were suggestive of NF-1. Doppler of left lower limb of same patient showed varicose veins. Doppler of other patient showed only muscle hypertrophy with no deeper vascular component.

Table 4: Demographic, clinical and imaging features of PPV

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age/ Sex	9y / Male	1.5y/Female	2 y/Female	1.5 y/Male	3y /Female
Cutaneous features	a)PWS- face, left side of trunk, left upper and lower limbs b)Dermal melancytosis- palate, left ear, trunk c)Melanosis oculi d) Multiple CALMs over trunk e)Mucosal	a)PWS-face, trunk and extremities b)Dermal melanocytosis- scalp, trunk,LL c)Melanosis oculi	a) PWS- Left LL b)Dermal melanocytosis- sacral area and buttocks	a)PWS-face, palate, buccal mucosa, left UL, both LL b)Dermal melanocytosis- trunk and extremities	a) CMTC- all over the body b)Dermal melanocytosis over left shoulder and lower back

	neuroma-tongue				
CNS symptoms	Nil	Nil	Nil	Seizures Developmental delay	Seizures
Eye	Bilateral Lisch nodules Bilateral glaucoma	Bilateral glaucoma	Normal	Bilateral buphthalmos-operated	Bilateral glaucoma
Other extracutaneous findings	-Left LL varicosities, hypertrophy	Macrocephaly	Left thigh muscle hypertrophy	Hypertrophy of right cheek, right arm and right thigh	-Macrocephaly -Left UL, LL hypertrophy
MRI Brain	-Foci of abnormal intensity in basal ganglia, cerebellar white matter -Moya moya phenomenon	-Dilated tortuous cerebral vessels - Mild atrophic changes of cerebrum	Not done	-Leptomeningeal angiomatosis -gyral calcification	-Leptomeningeal angiomatosis
Diagnosis	-PPV 2B with KTS -NF-1	PPV 2B with SWS	PPV 2A	PPV 2B with SWS	PPV 5B with SWS

Blue rubber bleb syndrome (BRBB)

A 6 year old boy who presented at 2 years of age with soft swelling over right thigh, bluish nodules over tongue, right elbow, both hands and palm was diagnosed with

BRBB. He had no significant eventful maternal antenatal history, exacerbating factors or extracutaneous features. MRI scan of left thigh showed multiple VM and phleboliths. Skin biopsy showed multiple dilated cavernous blood vessels lined by flattened to plump endothelial cells. Stool examination for occult blood was negative. Other lab parameters were normal.

CM- AVM syndrome

A 6 year old boy was diagnosed with CM-AVM syndrome. He had deep red macular area over right foot and sole since birth. The size of the right foot was gradually progressing and experienced bleeding on trauma. D-dimer levels were normal. X rays showed focal gigantism of right hallux. MRI showed underlying high flow malformation with intraosseous component.

Hereditary Hemorrhagic Telangiectasia (HHT)

HHT was found in a 48 year old lady. She had red papules over tongue, nasal mucosa and finger pulps. She noticed these lesions along with epistaxis at 40 years of her age. Similar features were found among her younger brother and father. She had gastrointestinal bleeding with hemoglobin of 9.5 g/dl and low PCV. Other lab parameters were normal. Ultrasound abdomen showed fibroid uterus. CT thorax ruled out AVM or pulmonary thromboembolism. It showed subsegmental atelectasis of left lower lobe of lung.

PIK3CA-Related Overgrowth Spectrum (PROS):

A 17 year old male patient was diagnosed with presumptive PROS. He was born to non-consanguineous couple, noticed lesions at birth with gradual progression. He did not have any complications or exacerbating factors.

He presented with following features compatible with the diagnosis of PROS

- Capillary malformation over right forearm and hand
- Epidermal nevus in Blaschkoid pattern over right forehead, right forearm, both legs along with ptychotropism
- Macrocephaly with head circumference of 63 cm
- Hemiatrophy of right sided face, skull, pinna and eye
- High arched palate
- Polydactyly (supernumerary digit) over right foot
- Left lower limb hypertrophy
- Biopsy showed features consistent with epidermal nevus

Table 5: Clinical features satisfying diagnostic criteria of PROS

Clinical diagnostic criteria	Clinical features in our patient
Congenital onset	Yes
Sporadic and mosaic overgrowth	Left – lower limb
Vascular malformations	Capillary malformation-right upper limb
Epidermal nevus (Biopsy proven)	Right forehead, forearm and both legs
Macrodactyly	-
Megalencephaly	Present (Right > left)

CLOVES syndrome

CLOVES syndrome is one of the entities resulting from PIK3CA mutations and is at present under umbrella term, PROS. Two patients with diagnosis of CLOVES syndrome were found. Both of them were male, born to non-consanguineous couple, noticed lesions at birth with gradual progression. They did not have any complications or exacerbating factors.

Table 7: Clinical and imaging features of CLOVES syndrome

Features of CLOVES syndrome	Case 1	Case 2
Congenital onset	Yes	Yes
Truncal Lipomatous mass	Mid and lower back	Mid back
Vascular malformations	Capillary malformation over scalp, chest, abdomen, back, palms and soles	Capillary malformation over left side of lower trunk
Epidermal nevus	Disseminated in Blaschkoid pattern sparing face	Nape of neck, left side of tongue and buccal mucosa
Skeletal abnormalities	Left trunk and lower limb over growth	Overgrowth of left hand fingers
Other features	Fissured tongue	Hypertrophy of left pinna and left cheek
Imaging	Normal	USG- small malrotated left kidney

Klippel-Trenaunay syndrome (KTS) [Table 6]

Frequency, gender and age distribution (demographic profile): Five patients were diagnosed with KTS. These were more common in females with male to female ratio of 1: 4. Mean age at presentation was 21 years.

Age of onset: Four patients with KTS noted lesions at birth. One girl noticed hypertrophy of right lower limb for the first time at 3.5 years of her age.

Anatomical distribution: Majority KTS (n=4, 80%) involved lower limbs. Among these patients, 3 patients had right lower limb involvement and one patient had left lower limb involvement. One patient with KTS of left upper limb had involvement of ipsilateral side of trunk with associated underlying lipomatous overgrowth. All the patients had capillary malformation over the affected limbs.

Complications: Two patients with KTS had history of bleeding from varicose veins on trivial trauma. Oozing was found in the patient with KTS involving left upper limb.

Extracutaneous features: All patients with KTS had overgrowth /hypertrophy of involved limb. Kyphoscoliosis was prominent in one patient with KTS of upper limb.

Associated features: One patient had acroangiodermatitis over the ipsilateral foot. Other patient had third toe macrodactyly of affected limb and syndactyly over contralateral limb. Ipsilateral lipomatous truncal overgrowth and macrodactyly of middle, ring and little fingers were found in the patient with left upper limb KTS.

Lab parameters: Three patients with KTS were found to have highly elevated D-dimer levels (> 1000 ng/ml). Other lab parameters were within normal limits.

Imaging studies: All the patients with KTS had undergone imaging studies. Doppler imaging and MRI scans were done in 4 patients and 3 patients respectively. Both imaging studies showed slow flow pattern in malformations. Majority patients (4 out of 5 patients) showed venous and lymphatic malformations in imaging whereas one patient had only venous malformation. Two patients had lateral marginal vein/ embryonic vein of affected limbs.

Table 6: Demographic, clinical and imaging features of KTS

Characteristics	**KTS**
Number of patients	5
Gender	M: F – 1: 4
Mean age of patients	21 years
Age of onset	At birth- 4 pts 1 pt- at 3.5 years
Location	Lower limbs- 4 pts (Right-3, Left-1) Upper limbs- 1 pt
Mucosal involvement	Nil
Complications	Bleeding- 2 pts Ooozing- 1 pt
Birth weight	LBW- 1 pt
Extracutaneous features	Limb hypertrophy- 5 pts Kyphoscoliosis- 1 pt
Lab parameters	D-dimer – elevated in 3 pts (>1000 ng/ml)
Imaging studies	Doppler – 4 pts MRI – 3 pts Results: VM + LM- 4 pts Only VM- 1 pt Lateral marginal vein – 2 pts

Table 8: Summary of imaging studies in vascular malformations

Vascular anomaly	Doppler US		MRI imaging		Role/ relevance
	Number	**Findings**	**Number**	**Findings**	
Simple CM (n =34)	3 1	Slow flow pattern with no deeper involvement Slow flow malformation with involvement of right side of face, right orbit and retromolar area.	-	-	Extent of lesion
Simple VM (n=10)	4	Slow flow malformations with venous flow	4	Cystic Vascular spaces with slow flow voids 1pt- intraosseus involvement 2pts- phleboliths	Diagnostic & extent of lesion
Simple LM (n=14)	4	Slow flow malformations with no blood flow	6	Vascular spaces with no flow voids	Diagnostic & extent of lesion
AVM (n=6)	4	High flow malformations	2	Cystic vascular spaces with high	Diagnostic &

				flow voids	extent of lesion
VLM (n=6)	5	Slow flow malformations with venous flow in few areas	4	Cystic vascular spaces with slow flow voids in few areas	Diagnostic & extent of lesion
KTS (n=5)	4	Slow flow malformations	3	Slow flow malformations and soft tissue/ skeletal hypertrophy. Lateral marginal vein in 2 patients	Diagnostic & extent of lesion
SWS (n=4)	-	-	4(MRI brain)	Leptomeningeal enhancement, dilated tortuous vessels, cerebral atrophic changes, gyral calcification	Diagnostic
PPV (n=5)	2	Varicose veins + hypertrophy in 1 patient. Only muscle hypertrophy in 1 patient	4(MRI brain)	One patient showed foci of abnormal intensity in basal ganglia & cerebellum, segmental narrowing of cerebral arteries All other patients showed features of SWS.	To look for associations
BRBB (n=1)	-		1	Multiple slow flow malformations with phleboliths	Diagnostic

Comparative profile of vascular tumours / vascular malformations in our study

[Table 9]

Table 9: Comparative profile of vascular tumours / vascular malformations

Characteristics	Vascular malformations (n, %)	Vascular tumours (n, %)	*p* value
Number of patients	88, 65%	48, 35%	-
M:F	1.26 : 1	1 : 4.3	<0.001
Mean age of patients	18.36 years	1.15 years	-
Mean age of onset	4 years	16th day	-
At birth	53, 61.6%	11, 22.4%	<0.001
Single lesions	60, 69.8%	43, 87.8%	0.021
H & N	33, 38.4%	34, 69.4%	0.001
UL	31, 36%	9, 18.4%	0.033
LL	25, 29.1%	5, 10.2%	0.017
Complications (most common)	Bleeding (21, 24.4%)	Ulceration (8, 16.3%)	-
CNS involvement	6, 7 %	3, 6.1%	1.000
Eye	5, 5.8%	2, 4.1%	1.000
Spine	3, 3.5%	1, 2%	1.000
Overgrowth	15, 17.6%	0	<0.001
Limb hypertrophy	15, 17.4%	-	0.001
Limb atrophy	2, 2.3%	-	0.534
D-dimer	7/14	2/3	0.550
Doppler	23 pts	4	<0.001

MRI	25 pts	2	<0.001

Vascular malformations were more common than vascular tumours in our study (65% vs 35%). Vascular malformations had slight male predominance with male to female ratio of 1.26: 1 while vascular tumours had clear female predilection with male-female ratio of 1: 4.3. Majority of vascular malformations were present at birth as opposed to vascular tumours (61.6% vs 22.4%). Significantly higher percentage of patients with vascular tumours (87.8% patients) presented with solitary lesions when compared to patients with vascular malformations who presented with multiple lesions (69.8% patients).(p= 0.021)

Head & neck (69.4%) was the commonest site of involvement in vascular tumour group whereas extremities (65.1%) were more frequently involved in vascular malformation group. Most common complication of vascular malformations was bleeding (24.4%) while ulceration (16.3%) was the most common complication of vascular tumours. The prevalence of CNS, eye and spinal abnormalities among vascular tumour and malformation groups were almost similar. However, there were significant proportion of patients with limb hypertrophy (17.4% patients) and limb atrophy (2.3% patients) in vascular malformation group while no such patients in vascular tumour group.

D-dimer levels were most commonly done in vascular malformations (14 patients) compared to vascular tumours (3 patients). Seven patients with vascular malformation and two patients with vascular tumour associated with coagulopathy had

elevated D-dimer levels. Skin biopsy (16 patients) was most commonly performed in vascular malformation group compared to vascular tumours (15 patients vs 1 patient). Lymphatic malformations (10 patients) were most common among vascular malformations to undergo biopsy.

Imaging studies were done predominantly in patients with vascular malformations. MRI (25 patients) was the commonest imaging modality used in vascular malformation group which helped in determining the extent of malformation. Others were Doppler (23 patients) and plain X-rays. Among Doppler studies, majority (21 patients) were abnormal and two were normal. Only 4 patients with isolated vascular tumours had Doppler done. MRI was done in 2 patients with PHACES syndrome**.**

DISCUSSION

Vascular anomalies represent a spectrum of disorders ranging from simple vascular nevus to life endangering entities.(1) These represent abnormalities due to defect in angiogenesis and vasculogenesis during embryo development.(11) The latest ISSVA classification of vascular anomalies was adopted in 2014.(5) Mutation analysis of vascular anomalies has been done in the recent times and various genetic mutations were listed in ISSVA classification. **[Appendix I (A)]** An emerging entity, PROS comprising of various overgrowth syndromes is not mentioned in the ISSVA classification of vascular anomalies. The estimated prevalence of cutaneous vascular anomalies in a study from the West was 4.55%.(6) The reported prevalence of vascular tumors and vascular malformations in the West was almost equal ranging from 30%-60% in case of vascular tumors and 30%-70% in case of vascular malformations.(2,13–15) In Asia, in contrast to this, in a study done in China on 592 patients with vascular anomalies, vascular malformations were more common than vascular tumors (68.4% vs. 31.6%).(7) There is a paucity of data on cutaneous vascular anomalies from Asia and the Indian subcontinent.(9,10) In India, two hospital based studies with small sample sizes showed contrasting results in terms of prevalence of vascular tumors and vascular malformations with 89.5% and 10.5% respectively in one study(10) with 19 subjects while 10% and 90% in another study with 20 subjects.(9)

This cross sectional study was done to address the lacunae in the data of the clinical profile of cutaneous vascular anomalies in India. In this study, vascular

malformations were present in 65% patients and vascular tumors in 35% patients which was similar to the data from an Asian study.(7) Among vascular malformations the most common entity seen in our study was capillary malformation while among vascular tumors the most common entity was infantile hemangioma. We found the prevalence of mixed vascular malformations of 5.1% to be similar to that of major studies on vascular anomalies where it was reported to be 2% -12.4%.(7,13,15) The prevalence of overgrowth syndromes in our study of 5.9%, was higher than that of a study reported from USA where it was found to be 3.5%.(13)

The comparative profile of various epidemiological studies on vascular anomalies is shown in **Table 10**

Table 10: Comparative profile of various epidemiological studies on vascular anomalies

Study group	**Mathes ED** (13) **(n = 175)**	**Fraulin** (15) **(n = 932)**	**YE Cai-sheng** (7) **(n = 592)**	**Mohammad Arif** (9) **(n = 20)**	**Senthil kumar**(10) **(n = 19)**	**Present study (n = 136)**
Country	US	Canada	China	India	India	India
Year	2001- 2003	1998-2009	2006-2009	2012-2013	2002-2004	2014-2016
Type of study	retrospective	Retrospective	Retrospective	Retrospective	cross sectional	cross sectional
Duration	2.5 yrs	11 yrs	3 yrs	1 year	2 years	2 years
No. of pts	175	932	592	20	19	136
Age- mean	17.9 yrs	-	14 yrs	25 yrs	1.3yrs	11.96yrs
M:F	61% -F	62%-F	54%- F	40%- F	68%- F	57%-F
Vascular tumours	28 (16%)	621(60.3%)	187(31.6%)	2 (10%)	17(89.5%)	48(35%)
Hemangiom -as	26 (14.8%)	621(60.3%)	181(30.4%)	2 (10%)	17(89.5%)	46(33.8%)
IH	24(13.7)	621(60.3%)	176(29.6%)	2 (10%)	17(89.5%)	42(30.9%)
Site	H&N-54(30.9%)	H&N- 54%	H&N-31.4%	H&N- 9 (45%)	-	H&N-32(76%)
PHACES	1 (0.6)	2(0.2%)	-	-	-	2(1.5%)
NICH	1 (0.6)	-	5 (0.8%)	-	-	1(0.74%)
RICH	-	-		-	-	3(2.2%)
KHE	2(1.2)	-	-	-	-	1(0.74%)
Tufted angioma	-	-	-	-	-	1(0.74%)
Vascular malf	71%	311(30.2%)	405(68.4%)	18(90%)	2(10.5%)	88(65%)
capillary malf	3(1.7)	98 (10.50%)	21(3.6%)	2(10%)	2(10.5%)	34(25%)
SWS	1(0.6)	3 (0.32%)	-	-	-	4(2.94%)
PPV	-	-	-	-	-	5(3.7%)
venous malf	62 (35.0)	121 (13%)	166(28%)	13(65%)	-	10(7.4%)
BRB nevus syn	1(0.6)	-	-	-	-	1(0.74%)
Lymph malf	13(7.4)	36 (3.9 %)	5(0.8%)	-	-	14(10.3%)
mixed	18(10.3)	18 (2%)	73(12.4%)	1(5%)	-	7 (5.1%)
KTS	8 (4.6)	25 (2.7%)	2 (0.3%)	-	-	5(3.7%)
Proteus like syn	6(3.5)	-	-	-	-	CLOVES-2(1.5%) PROS-1(0.74%)

AVM	9(5.1)	9 (0.96%)	79(13.3%)	2(10%)	-	6(4.4%)
Parkes weber	1(0.6)	-	-	-	-	-

Vascular tumours

Vascular tumours found in our study were IH, congenital hemangiomas, TA and KHE. Universally vascular tumours have a clear female predilection with male-female ratio of 1:3- 1:9 in Western countries(2) and 1: 1.49 in Asia(7).

Data from our study showed that IH was the most common vascular tumour with the prevalence comparable to that of a large study conducted in the US (88% vs 85.9%)(2) Clinical profile of IH in our study was similar to the other studies(15,19,20) with female preponderance, head and neck being the most common site of involvement and ulceration being the most common complication. 14.3% of patients gave a history of prematurity and low birth weight, this was slightly higher than that reported in literature of 8.7%-9.1%.(19) The proportion of patients with PHACES syndrome in our study was 1.5% which was higher than that reported in a study from Canada with 932 subjects in which the prevalence was found to be 0.2%.(15) The spectrum of findings in our cases of PHACES syndrome was similar to that reported in other studies except for the absence of cardiovascular anomalies in our patients.(33)

We also found that the prevalence of congenital hemangiomas to be 2.9% which was higher than that reported in literature of 0.6%- 0.8%.(7,13) Among congenital hemangiomas, RICH was more common than NICH with the ratio of 3:1 in our study.

NICH and RICH should be suspected when patients present with full sized red swelling at birth. These could be further differentiated based on the clinical behaviour, as RICH had history of involution while NICH was stable or proportionate growth. RICH also have a typical perilesional ring of pallor, seen in 2 of our cases.(120)

TA and KHE are rare vascular tumours and was seen in one patient each in our study. Both conditions show a male predominance.(45,47) However, in our study, both the cases were female. Hypertrichosis and hyperhidrosis often reported over the lesions were not found in our cases.(45) Though highly elevated D-dimer levels found in both the cases, only KHE had KMP with severe thrombocytopenia in our study. The prevalence of KMP in cases of KHE was 71% as per the data from a published study with 107 subjects.(47) TA and KHE are to be suspected when patients present with a congenital dusky red to violaceous indurated mass. The associated Kasabach-Meritt syndrome is to be suspected whenever patients have sudden increase in size of these indurated lesions with tenderness and are to be screened with coagulation profile including D-dimers.

In our study the other distinctive features of vascular tumours as opposed to malformations other than those mentioned were occurrence later in the neonatal period rather than at birth and absence of limb hypertrophy or other tissue overgrowth.

Vascular malformations

Among vascular malformations, slow flow malformations were predominant in present study which was similar to that of literature.(2,7,13,15,121) Among them, capillary malformations were the most common vascular malformations in our study while in the West (13–15) and other Asian countries like China (121) , venous & lymphatic malformations were the most common malformations. [**Table 10**] PPV and PROS which were not described in the other studies (7,9,10,13,15) were found in 4 and 3 patients respectively in our study. [**Table 10]**

In our study, a male preponderance was found among capillary malformations as opposed to the literature where slight female predominance was reported.(55,89) Majority of capillary malformations were seen at birth in our study except for the 3 acquired PWS. Acquired PWS is an uncommon entity and less than 75 cases have been reported in literature.(57–60) Trauma, the most common antecedent factor was present in 2 patients with acquired PWS in our study which was similar to the published literature.(58) As mentioned in literature, the proposed mechanisms of acquired PWS could be alteration in capillary neural tone or dragging of attention of patient/ guardian after an antecedent trauma.(58) Pregnancy was the triggering factor in one patient. The site of occurrence the head & neck region and the age of presentation in the third decade of capillary malformations was similar to other studies.(15,55,89) In our study, 79% of simple capillary malformations were non-syndromic and 21% of cases were syndromic as opposed to the data from the US study where there was high proportion of isolated cases vs syndromic capillary malformations (97% vs 3%).(15) This apparent discrepancy may

be because our hospital is referral center for intervention in vascular anomalies. In published data on vascular malformations the only syndromic variant reported was SWS.(7,13,15) However, in our study additionally there were 4 cases of PPV and one case of HHT.

Around 250 cases of PPV have been reported to date.(108,122,123) There are few anecdotal case series and case reports of PPV from India. PPV type 2b was the commonest subtype in our study which was similar to the literature.(108,122) Two of these cases were associated with SWS and one with KTS and NF-1. The latter association has not been reported in literature.

Among extracutaneous features described in association with capillary malformations in literature glaucoma was the most common.(89) However, in our study we found CNS to be the most common extracutaneous system involved which manifested as seizures. Glaucoma was found in 7.5% of our patients with capillary malformations. MRI imaging of all SWS patients showed typical features of leptomeningeal angiomatosis, cerebral atrophic changes and gyral calcification as mentioned in literature.(96–98) It is noteworthy that one of the patients in our study, a 25 year old gentleman with isolated capillary malformation was found to have hemangiomas of liver in imaging studies. This combination was not reported in literature till date.

In our study, contrary to the Indian and western studies, the prevalence of venous malformations was lower than that of capillary malformations **(Table 10)** The gender distribution of female predominance & involvement of lower limbs were similar to other studies on venous malformations.(2,13,21,66) Among simple venous malformations, 91% were isolated or common , 9% were syndromic which was comparable to the data of a study from Canada where 94% were isolated and 6% were syndromic.(13) One syndromic case in our study was BRBB syndrome. There are few anecdotal case reports of BRBB in literature and around 200 cases are reported in world literature.(124–126) The BRBB case in our study presented with multiple venous malformations over skin, oral mucosa and palms. Involvement of palms along with multiple mucocutaneous sites in BRBB syndrome was typically reported in the literature.(96)

Elevated D-dimer level that indicates localized intravascular coagulopathy, is highly specific of VM and therefore is an easy biomarker test to identify them.(127) The data from the French study showed that 42% venous malformation cases had elevated D-dimer levels.(66) High D-dimer levels correlated with venous malformations with large surface area and phleboliths.(66) We estimated D-dimer levels in those at risk for thrombosis. Of them 75% had elevated D-dimer levels (>250 ng/ml) of which one patient had highly elevated D-dimer levels (>1000 ng/ml) and was started on low molecular weight heparin. Doppler and MRI were commonly performed in venous malformation cases. Both imaging studies showed slow flow malformations with venous flow in the

cysts/ cavities which was comparable to the literature.(13,18,128) MRI imaging of BRBB case showed multiple slow flow malformations with venous flow and phleboliths in our study.

LM were present in 10.3% patients in our study. They differed from the features of LM in published literature as there was a higher prevalence, more frequent occurrence over the trunk Vs the head & neck and the microcystic type was more common than macrocystic and mixed varieties which were reported in equal proportion in a study from Korea.(6,8,81) The gender distribution of male preponderance in our study was similar to other studies on lymphatic malformations.(2,13,73) Extracutaneous involvement was present only in 1 patient as opposed to a study from Canada where 10% had involvement of viscera.(73) Both MRI and ultrasound examination of LMs in our study showed slow flow vascular malformation with no blood flow in LM except in septae. MRI was preferred to ultrasound due to its superiority in determining the extent and invasiveness of the lesion.(129)

AVM are relatively uncommon among vascular anomalies with the prevalence of 0.96%- 5.10% in the literature.(13,15) In our study 4.4% patients had AVM. Although no gender bias has been reported in the literature (2,15) we found that males were predominantly affected with male to female ratio of 5 : 1. Head and neck region was the most common site involved by AVM which was similar to the literature.(85,87) AVM were apparent at birth in a third of patients which was slightly lower than the reported prevalence of 40%-59% in studies done in France and US.(85,87) One case of

capillary malformation-arteriovenous malformation (CM-AVM/ CAVM) was found in our study and was associated with macrodactyly of hallux. This patient differed from the classical description of CM-AVM syndrome in literature in which multiple small, round to oval capillary malformations are seen in association with AVM.(117) Our case had only a solitary capillary malformation in combination with AVM. AVMs are known to be exacerbated at puberty which was seen in one of our patients.(85,87). Cardiac decompensation was not seen in our patients. The most commonly reported extracutaneous system involved in literature was the skeletal system, one of our patients had macrodactyly.(85) Imaging studies of AVM were in agreement with and confirmed the clinical diagnosis in our cases, all of whom had a bruit on palpation. Doppler was the most common imaging modality used in our study which showed fast flow malformation and this was in line with other studies.(85,87)

The prevalence and gender distribution of combined vascular malformations in our study was similar to other studies from the West where the prevalence of 2%-10.3% and no gender bias have been reported.(2,13,15) In our study, among combined malformations, majority were VLM. This is different from the data of study from China where they found various combinations of malformations- CVM (58.6%) was the highest and VLM accounted for only 8% of cases. VLM should be suspected when patient presents with compressible bluish masses along with areas of grouped clear or hemorrhagic vesicles. As reported in literature combined vascular malformations were relatively more prone to complications than isolated vascular malformations.(15) The

most common complication noted was bleeding. Although involvement of viscera by combined vascular malformations was not specified in other studies, in our study we found that 2 VLM patients had extensive intraabdominal and pelvic involvement.(13,15) In one patient, VLM involved lower abdominal mesentery, sigmoid mesocolon, superior wall of urinary bladder, bilateral ischiorectal fossae and abutted right adrenal gland. In other patient, VLM involved recto-sigmoid region, right parametrium till pelvic side wall. Doppler US and MRI examination of VLM showed combined features of venous malformation and lymphatic malformations (as mentioned in respective sections). Highly elevated D-dimer levels was seen in one patient, this indicated predominance of venous component in the combined malformation as mentioned in the literature.(130)

Overgrowth syndromes

Overgrowth syndrome, a newly emerging entity, is a rare condition associated with vascular malformations. PROS is a newly proposed umbrella term that includes CLOVES syndrome, HHML, facial infiltrating lipomatosis, M-CM syndrome, fibroadipose overgrowth or hyperplasia (FAO), macrodactyly and muscle hemihypertrophy, skin disorders like epidermal nevi, seborrhoeic keratosis and benign lichenoid keratosis.(119) There is still a debate whether KTS comes under the group PROS, as *PIK3CA* mutations have been detected in few KTS like phenotypes. (131) There are only few case series in world literature on various entities that now come under PROS.(132–135) However, these conditions were not reported in large

studies on vascular anomalies except from the study done in US by Mathes et al, where 6 cases of Proteus like syndromes (specific diagnosis was not mentioned) were reported, among which few cases might be of PROS.(13) The advantage of grouping these overgrowth syndromes under PROS is that PIK3 inhibitors like BEZ235 and PX-286 might have therapeutic applications for this group.(136,137) In our study, 3 patients had clinical features compatible with PROS.

CLOVES syndrome is very rare and only few anecdotal reports with small cohorts are reported in literature.(132,134,135,137) In our study we found 2 cases of CLOVES syndrome which has not been reported in major studies on vascular anomalies.(7,13,15) This might be due to increased awareness and knowledge of these rare overgrowth syndromes in the recent times and also due to large referral base. The spectrum of clinical features of our patients with CLOVES syndrome was similar to that of published literature with congenital onset of asymmetric lipomatous overgrowth that is proportionate in nature, epidermal nevus and skeletal abnormalities.(132,134,135)

In our study, KTS was found in 5 cases (3.7% patients). This proportion was high compared to a study from China (0.3% patients) but was similar to the Western studies (2.7%-4.6% patients).(7,13,15) Female predominance was high among KTS patients in our study (M:F- 1:4) while equal gender distribution was reported in a study by Jacob et al on KTS.(100) Similar to them, the lower limb was the commonest site involved and bleeding was the most common complication of KTS.(100) However in that study, all three essential components (CM, VM, limb hypertrophy) were found only

in 63% of KTS patients and lateral marginal vein was detected in 11.5%.(100) In our study all patients had all three essential components and lateral marginal vein was detected in 40% of KTS patients. The presence of lateral marginal veins indicates the result of genetic defect leading to the formation of abnormal venous pattern in KTS.(138)

In our study overgrowth was found in conditions other than PROS, like PPV (3 cases), CM-AVM(1 case), simple VM(2 cases), combined VLM (2 cases), PWS(1 case) and CMTC(1 case).

In summary, vascular malformations were the predominant vascular anomaly in our study which is in concordance with majority of studies.(2,7,9,13) Capillary malformation was the most common. In contrast, most studies report a higher prevalence of venous malformations.(2,7,13,15) 22.7% were found to be syndromic. The proportion of overgrowth syndromes was higher in our group as compared to literature.(13)

CONCLUSIONS

- Vascular malformations were more prevalent than vascular tumours.
- Majority vascular malformations were present at birth as opposed to IH (representing majority of vascular tumours) which had a later onset, usually by one month of age (83.3%)
- The vascular tumours in our study included IH, RICH, NICH, TA and KHE.
- Female preponderance was noted in all types of vascular tumours.
- IH was the most common cutaneous vascular tumour and accounted for 88% vascular tumours
- Most of IH involved head and neck region accounting for 76% patients, the most common complication was ulceration.
- PHACES syndrome was noted in 2 patients with large facial IH involving posterior fossa structural and cerebrovascular abnormalities.
- The only case of KHE in our study was associated with KMP
- The vascular malformations in our study included capillary malformations, VM, LM, AVM, combined malformations and associated syndromes
- Male preponderance was noted in all subtypes of vascular malformations except venous malformations where females were predominant.
- Capillary malformation was the most prevalent subtype of vascular malformation in our study followed by LM and venous malformation.

- SWS, PPV and HHT were rare syndromic variants of capillary malformation
- Overgrowth and limb abnormalities including hypertrophy and atrophy were exclusively associated with vascular malformations rather than vascular tumours.
- Three patients were classified as PROS which included 2 patients of CLOVES.
- The other overgrowth syndrome, KTS was found in five patients
- Among vascular malformations, elevated D-dimer levels were found in simple venous malformations, VLM and KTS
- Imaging studies were done in patients with vascular malformations for the precise diagnosis and also to look for the extent of the lesions.

LIMITATIONS

- The study is from a single tertiary care centre, therefore the sample may not be representative of a large population
- This is a cross sectional descriptive study. Hence we could not study the role of various interventions and prognosis of the disease enitities.
- Imaging studies are done only wherever necessary, therefore there may be chance of missing few vascular anomalies.

RECOMMENDATIONS

- Multicentre studies are needed to study the prevalence and clinical profile of cutaneous vascular anomalies in India
- A prospective study on various intervention modalities should be done to aim to decrease the morbiditiy of the disease in patients with vascular anomalies

SUMMARY

Background

The estimated prevalence of vascular anomalies in world literature is 4.55%. Cutaneous vascular anomalies comprise of vascular tumours and vascular malformations which are distinct entities differing in clinical profile, course, prognosis and treatment. There is limited data on these entities from India. This study was undertaken to address the lacunae in the data of the clinical profile of vascular anomalies.

Objective

Our primary objective was to study the clinical features of cutaneous vascular anomalies. Secondary objective was to describe the overgrowth syndromes and extracutaneous features of vascular anomalies.

Methods: A hospital based cross sectional study was conducted in the department of Dermatology, Venereology and Leprosy, Christian Medical College, Vellore over period of 23 months with approval from the Institution Review Board (IRB.No: 9082). Patients with clinical features of cutaneous vascular anomalies were included in the study. Patients were informed prior to inclusion in the study and a written consent was obtained from the patients and guardians in case of children. Demographic details, clinical data, laboratory values, imaging and histopathological findings were recorded in a proforma.

Skin biopsies were done in few doubtful cases. Immunohistochemical marker (D2-40) was used in few doubtful cases of LM. Imaging studies were done in majority patients wherever necessary to confirm the diagnosis and extent of involvement of vascular anomalies as a part of standard operating procedures. Patients were classified according to the ISSVA classification [Annexure I(A)]. Patients with PROS, an emerging entity were diagnosed based on the clinical diagnostic criteria of PROS that were described in the consensus document [Annexure-I(D)]. Data on clinical and radiological features were expressed in numbers and percentages. *P* value was calculated using Fisher's exact test wherever applicable.

Results: A total of 136 patients with cutaneous vascular anomalies were included in the study. There were a total of 60 males and 76 females (M:F-1:1.25). The mean age of patients presented with vascular anomalies was 11.96±16.61yrs (range 1 month-73years). Vascular malformations (n=88, 65%) were more common as compared to vascular tumours (n=48, 35%). Vascular tumours had clear female preponderance with 39 female and 9 males (M:F = 1: 4.3). IH (n=42,30.9%) was the most common vascular tumour followed by RICH (n=3, 2.2%), NICH (n=1, 0.74%), TA (n=1, 0.74%) and KHE (n=1, 0.74%). The only syndrome associated with IH in our study was PHACES syndrome found in 2 patients. Vascular malformations had male preponderance with 49 males and 39 females (M:F= 1.26: 1). The most common type of vascular malformation was capillary malformation (n=34, 25%) followed by LM (n=14, 10.3%), VM (n=10, 7.4%),

mixed vascular malformations (n=7,5.1%) and AVM (n=6, 4.4%). The rare overgrowth syndromes found in our study were PROS (n=3, 2.2%) including CLOVES syndrome. Five patients had KTS (3.7%). The other rare syndromes associated with vascular malformations were PPV (n=5, 3.7%), SWS (n=4, 2.94%), HHT (n=1, 0.74%) and BRBB (n=1, 0.74%). Head & neck was the commonest location of capillary malformations and AVM whereas trunk and extremities were the predominant locations of LM and VM respectively. The extracutaneous systems involved in our patients with vascular anomalies were skeletal system (21, 15.4%), CNS (9, 6.6%), eye (7, 5.15%) and abdomen (3, 2.2%). Skin biopsies were done in LM (6), VLM(4), VM (3), CM (2), epidermal nevus (2) and TA(1). D-dimer levels were done in 17 patients out of which 9 patients had elevated levels. MRI and Doppler US were done in 27 patients each. Lateral marginal veins and phleboliths were found in 3 patients each.

Conclusion: In our study of 136 patients with cutaneous vascular anomalies, vascular malformations were more commoner than vascular tumours. Majority vascular malformations were present at birth as opposed to IH (representing majority of vascular tumours) which appeared later. Female preponderance was noted in all subtypes of vascular tumours. IH was the most common cutaneous vascular tumour and accounted for 88% vascular tumours. Most of the IH involved head and neck region accounting for 76% patients. PHACES syndrome was found in 2 patients with large facial IH. Although elevated D-dimer levels were found in TA and KHE, only KHE was associated with KMP. Male preponderance was noted in all subtypes of vascular malformations except

venous malformations where females were predominant. Capillary malformation was the most prevalent subtype of vascular malformation in our study followed by LM and venous malformation. SWS, PPV and HHT were rare syndromic variants of capillary malformation. The proportion of overgrowth disorders, including PROS, CLOVES syndrome and KTS was relatively higher in our study as compared to that of large studies on vascular anomalies. Among vascular malformations, elevated D-dimer levels were found in simple venous malformations, VLM and KTS. MRI was the commonest imaging modality used among vascular malformations. Other imaging modalities used were Doppler US and plain X rays. Multicenter studies are needed to study the prevalence and clinical profile of cutaneous vascular anomalies in India.

REFERENCES

1. Wassef M, Blei F, Adams D, Alomari A, Baselga E, Berenstein A, et al. Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. Pediatrics. 2015 Jun 1;peds.2014-3673.

2. Greene AK. Vascular Anomalies: Current Overview of the Field. Clin Plast Surg. 2011 Jan;38(1):1–5.

3. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982 Mar;69(3):412–22.

4. Hand JL, Frieden IJ. Vascular birthmarks of infancy: resolving nosologic confusion. Am J Med Genet. 2002 Apr 1;108(4):257–64.

5. Diapositive 1 - docs.ashx [Internet]. [cited 2014 Aug 16]. Available from: http://issva.clubexpress.com/docs.ashx?id=178348

6. Greene AK, Kim S, Rogers GF, Fishman SJ, Olsen BR, Mulliken JB. Risk of Vascular Anomalies With Down Syndrome. Pediatrics. 2008 Jan 1;121(1):e135–40.

7. Ye C-S, Pan L-X, Huang Y-B, Han A-J, Ye R-Y, Li S-Q, et al. Clinical analysis of vascular anomalies: a hospital-based retrospective study of 592 patients in southeast China. Chin Med J (Engl). 2011 Oct;124(19):3008–12.

8. Yang B, Li L, Zhang L, Sun Y, Ma L. Clinical Characteristics and Treatment Options of Infantile Vascular Anomalies. Medicine (Baltimore). 2015 Oct;94(40):e1717.

9. Mohammed A. Clinical Characteristics and Management of Vascular Anomalies: Our Institutional Experience. Head Neck. 9:45.

10. Thappa D, Senthilkumar M. Vascular nevi in children. Indian J Dermatol Venereol Leprol. 2006;72(1):19.

11. Dohil MA, Baugh WP, Eichenfield LF. Vascular and pigmented birthmarks. Pediatr Clin North Am. 2000 Aug;47(4):783–812, v–vi.

12. Kollipara R, Odhav A, Rentas KE, Rivard DC, Lowe LH, Dinneen L. Vascular Anomalies in Pediatric Patients: Updated Classification, Imaging, and Therapy. Radiol Clin North Am. 2013 Jul;51(4):659–72.

13. Mathes ED, Haggstrom AN, Dowd C, Hoffman WY, Frieden IJ. Clinical characteristics and management of vascular anomalies: Findings of a multidisciplinary vascular anomalies clinic. Arch Dermatol. 2004 Aug 1;140(8):979–83.

14. Upton J, Coombs CJ, Mulliken JB, Burrows PE, Pap S. Vascular malformations of the upper limb: A review of 270 patients. J Hand Surg. 1999 Sep;24(5):1019–35.

15. Fraulin FO, Flannigan RK, Sharma VK, McPhalen DF, Harrop RA. The epidemiological profile of the Vascular Birthmark Clinic at the Alberta Children's Hospital. Can J Plast Surg. 2012;20(2):67–70.

16. Chiller KG, Passaro D, Frieden IJ. Hemangiomas of infancy: clinical characteristics, morphologic subtypes, and their relationship to race, ethnicity, and sex. Arch Dermatol. 2002 Dec;138(12):1567–76.

17. Mendiratta V, Jabeen M. Infantile hemangioma: An update. Indian J Dermatol Venereol Leprol. 2010;76(5):469.

18. Lowe LH, Marchant TC, Rivard DC, Scherbel AJ. Vascular malformations: classification and terminology the radiologist needs to know. Semin Roentgenol. 2012 Apr;47(2):106–17.

19. Li J, Chen X, Zhao S, et al. Demographic and clinical characteristics and risk factors for infantile hemangioma: A chinese case-control study. Arch Dermatol. 2011 Sep 1;147(9):1049–56.

20. Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, Horii KA, et al. Prospective Study of Infantile Hemangiomas: Demographic, Prenatal, and Perinatal Characteristics. J Pediatr. 2007 Mar;150(3):291–4.

21. Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations. J Am Acad Dermatol. 2007 Mar 1;56(3):353–70.

22. Karthikeyan K, Thappa DM, Jeevankumar B. Pattern of pediatric dermatoses in a referral center in South India. Indian Pediatr. 2004 Apr;41(4):373–7.

23. Chang LC, Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, et al. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics. 2008 Aug;122(2):360–7.

24. Amir J, Metzker A, Krikler R, Reisner SH. Strawberry hemangioma in preterm infants. Pediatr Dermatol. 1986 Sep;3(4):331–2.

25. Luu M, Frieden I j. Haemangioma: clinical course, complications and management. Br J Dermatol. 2013 Jul 1;169(1):20–30.

26. Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, Horii KA, et al. Prospective Study of Infantile Hemangiomas: Clinical Characteristics Predicting Complications and Treatment. Pediatrics. 2006 Sep 1;118(3):882–7.

27. North PE, Waner M, Mizeracki A, Mihm MC. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol. 2000 Jan;31(1):11–22.

28. Leon-Villapalos J, Wolfe K, Kangesu L. GLUT-1: an extra diagnostic tool to differentiate between haemangiomas and vascular malformations. Br J Plast Surg. 2005 Apr;58(3):348–52.

29. Dickie B, Dasgupta R, Nair R, Alonso MH, Ryckman FC, Tiao GM, et al. Spectrum of hepatic hemangiomas: management and outcome. J Pediatr Surg. 2009 Jan;44(1):125–33.

30. Liang MG, Frieden IJ. Infantile and congenital hemangiomas. Semin Pediatr Surg. 2014 Aug;23(4):162–7.

31. Frieden IJ, Reese V, Cohen D. PHACE syndrome. The association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. Arch Dermatol. 1996 Mar;132(3):307–11.

32. Metry D, Heyer G, Hess C, Garzon M, Haggstrom A, Frommelt P, et al. Consensus Statement on Diagnostic Criteria for PHACE Syndrome. Pediatrics. 2009 Nov 1;124(5):1447–56.

33. Haggstrom AN, Garzon MC, Baselga E, Chamlin SL, Frieden IJ, Holland K, et al. Risk for PHACE Syndrome in Infants With Large Facial Hemangiomas. Pediatrics. 2010 Aug 1;126(2):e418–26.

34. Winter PR, Itinteang T, Leadbitter P, Tan ST. PHACE syndrome – clinical features, aetiology and management. Acta Paediatr. 2016 Feb 1;105(2):145–53.

35. Iacobas I, Burrows PE, Frieden IJ, Liang MG, Mulliken JB, Mancini AJ, et al. LUMBAR: Association between Cutaneous Infantile Hemangiomas of the Lower Body and Regional Congenital Anomalies. J Pediatr. 2010 Nov;157(5):795–801.e7.

36. Boon LM, Enjolras O, Mulliken JB. Congenital hemangioma: Evidence of accelerated involution. J Pediatr. 1996 Mar;128(3):329–35.

37. Browning JC, Metry DW. Rapidly involuting congenital hemangioma: case report and review of the literature. Dermatol Online J. 2008;14(4):11.

38. Lee PW, Frieden IJ, Streicher JL, McCalmont T, Haggstrom AN. Characteristics of noninvoluting congenital hemangioma: A retrospective review. J Am Acad Dermatol. 2014 May;70(5):899–903.

39. Nasseri E, Piram M, McCuaig CC, Kokta V, Dubois J, Powell J. Partially involuting congenital hemangiomas: A report of 8 cases and review of the literature. J Am Acad Dermatol. 2014 Jan;70(1):75–9.

40. Vildy S, Macher J, Abasq-Thomas C, et al. Life-threatening hemorrhaging in neonatal ulcerated congenital hemangioma: Two case reports. JAMA Dermatol. 2015 Apr 1;151(4):422–5.

41. Baselga E, Cordisco M r., Garzon M, Lee M t., Alomar A, Blei F. Rapidly involuting congenital haemangioma associated with transient thrombocytopenia and coagulopathy: a case series. Br J Dermatol. 2008 Jun 1;158(6):1363–70.

42. Rogers M, Lam A, Fischer G. Sonographic findings in a series of rapidly involuting congenital hemangiomas (RICH). Pediatr Dermatol. 2002 Feb;19(1):5–11.

43. Elia D, Garel C, Enjolras O, Vermouneix L, Soupre V, Oury J-F, et al. Prenatal imaging findings in rapidly involuting congenital hemangioma of the skull. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2008 May;31(5):572–5.

44. Jones EW, Orkin M. Tufted angioma (angioblastoma). A benign progressive angioma, not to be confused with Kaposi's sarcoma or low-grade angiosarcoma. J Am Acad Dermatol. 1989 Feb;20(2 Pt 1):214–25.

45. Osio A, Fraitag S, Hadj-Rabia S, Bodemer C, de Prost Y, Hamel-Teillac D. Clinical spectrum of tufted angiomas in childhood: A report of 13 cases and a review of the literature. Arch Dermatol. 2010 Jul 1;146(7):758–63.

46. Zukerberg LR, Nickoloff BJ, Weiss SW. Kaposiform hemangioendothelioma of infancy and childhood. An aggressive neoplasm associated with Kasabach-Merritt syndrome and lymphangiomatosis. Am J Surg Pathol. 1993 Apr;17(4):321–8.

47. Croteau SE, Liang MG, Kozakewich HP, Alomari AI, Fishman SJ, Mulliken JB, et al. Kaposiform Hemangioendothelioma: Atypical Features and Risks of Kasabach-Merritt Phenomenon in 107 Referrals. J Pediatr. 2013 Jan;162(1):142–7.

48. Croteau SE, Kozakewich HPW, Perez-Atayde AR, Fishman SJ, Alomari AI, Chaudry G, et al. Kaposiform lymphangiomatosis: a distinct aggressive lymphatic anomaly. J Pediatr. 2014 Feb;164(2):383–8.

49. Rendón-Elías FG, Hernández-Sánchez M, Albores-Figueroa R, Montes-Tapia FF, Gómez-Danés LH. Congenital vascular malformations update. Med Univ. 2014 Oct 1;16(65):184–98.

50. Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: clinical application of a new classification. J Pediatr Surg. 1983 Dec;18(6):894–900.

51. Güneyli S, Ceylan N, Bakraktaroğlu S, Acar T, Savaş R. Imaging findings of vascular lesions in the head and neck. Diagn Interv Radiol Ank Turk. 2014 Jun 19;

52. Legiehn GM, Heran MKS. Classification, diagnosis, and interventional radiologic management of vascular malformations. Orthop Clin North Am. 2006 Jul;37(3):435–474, vii–viii.

53. Dubois J, Garel L. Imaging and therapeutic approach of hemangiomas and vascular malformations in the pediatric age group. Pediatr Radiol. 1999 Dec;29(12):879–93.

54. Hideki Hyodoh MH. Peripheral vascular malformations: imaging, treatment approaches, and therapeutic issues. Radiogr Rev Publ Radiol Soc N Am Inc. 2005;25 Suppl 1:S159-71.

55. Barsky SH, Rosen S, Geer DE, Noe JM. The Nature and Evolution of Port Wine Stains: A Computer-assisted Study. J Invest Dermatol. 1980 Mar;74(3):154–7.

56. Klapman MH, Yao JF. Thickening and nodules in port-wine stains. J Am Acad Dermatol. 2001 Feb;44(2):300–2.

57. Bansal S, Garg V, Wadhwa B, Khurana N. Acquired port-wine stain in an adult male: First reported case from India with review of literature. Indian J Dermatol. 2015;60(1):104.

58. Adams BB, Lucky AW. Acquired port-wine stains and antecedent trauma: Case report and review of the literature. Arch Dermatol. 2000 Jul 1;136(7):897–9.

59. Hoque S, Holden C. Acquired port wine stain following oral isotretinoin. Clin Exp Dermatol. 2005 Sep;30(5):587–8.

60. Rose RF, Merchant W, Wilkinson SM. Acquired port-wine stain occurring in association with a congenital lesion. Clin Exp Dermatol. 2011 Aug 1;36(6):621–3.

61. Shirley MD, Tang H, Gallione CJ, Baugher JD, Frelin LP, Cohen B, et al. Sturge–Weber Syndrome and Port-Wine Stains Caused by Somatic Mutation in GNAQ. N Engl J Med. 2013 May 23;368(21):1971–9.

62. Devillers AA, de Waard-van der Spek FB, Oranje AP. Cutis marmorata telangiectatica congenita: Clinical features in 35 cases. Arch Dermatol. 1999 Jan 1;135(1):34–8.

63. Amitai DB, Fichman S, Merlob P, Morad Y, Lapidoth M, Metzker A. Cutis marmorata telangiectatica congenita: clinical findings in 85 patients. Pediatr Dermatol. 2000 Apr;17(2):100–4.

64. Dubois J, Soulez G, Oliva VL, Berthiaume M-J, Lapierre C, Therasse E. Soft-Tissue Venous Malformations in Adult Patients: Imaging and Therapeutic Issues. RadioGraphics. 2001 Nov 1;21(6):1519–31.

65. Enjolras O, Mulliken JB. The current management of vascular birthmarks. Pediatr Dermatol. 1993 Dec;10(4):311–3.

66. Dompmartin A, Acher A, Thibon P, et al. ASsociation of localized intravascular coagulopathy with venous malformations. Arch Dermatol. 2008 Jul 1;144(7):873–7.

67. Zheng JW, Mai HM, Zhang L, Wang YA, Fan XD, Su LX, et al. Guidelines for the treatment of head and neck venous malformations. Int J Clin Exp Med. 2013 May 22;6(5):377–89.

68. Mazoyer E, Enjolras O, Bisdorff A, Perdu J, Wassef M, Drouet L. Coagulation disorders in patients with venous malformation of the limbs and trunk: A case series of 118 patients. Arch Dermatol. 2008 Jul 1;144(7):861–7.

69. Hyodoh H, Hori M, Akiba H, Tamakawa M, Hyodoh K, Hareyama M. Peripheral Vascular Malformations: Imaging, Treatment Approaches, and Therapeutic Issues. RadioGraphics. 2005 Oct 1;25(suppl_1):S159–71.

70. Brouillard P, Boon LM, Mulliken JB, Enjolras O, Ghassibé M, Warman ML, et al. Mutations in a Novel Factor, Glomulin, Are Responsible for Glomuvenous Malformations ("Glomangiomas"). Am J Hum Genet. 2002 Apr;70(4):866–74.

71. Boon LM, Mulliken JB, Enjolras O, Vikkula M. Glomuvenous malformation (glomangioma) and venous malformation: distinct clinicopathologic and genetic entities. Arch Dermatol. 2004 Aug;140(8):971–6.

72. Redondo P. [Classification of vascular anomalies (tumours and malformations). Clinical characteristics and natural history]. An Sist Sanit Navar. 2004;27 Suppl 1:9–25.

73. Alqahtani A, Nguyen LT, Flageole H, Shaw K, Laberge J-M. 25 Years' experience with lymphangiomas in children. J Pediatr Surg. 1999 Jul;34(7):1164–8.

74. Padwa BL, Hayward PG, Ferraro NF, Mulliken JB. Cervicofacial lymphatic malformation: clinical course, surgical intervention, and pathogenesis of skeletal hypertrophy. Plast Reconstr Surg. 1995 May;95(6):951–60.

75. Greene AK, Burrows PE, Smith L, Mulliken JB. Periorbital lymphatic malformation: clinical course and management in 42 patients. Plast Reconstr Surg. 2005 Jan;115(1):22–30.

76. Marler JJ, Mulliken JB. Current management of hemangiomas and vascular malformations. Clin Plast Surg. 2005 Jan;32(1):99–116.

77. Wilson G r., Cox N h., Mclean N r., Scott D. Squamous cell carcinoma arising within congenital lymphangioma circumscriptum. Br J Dermatol. 1993 Sep 1;129(3):337–9.

78. Schook CC, Mulliken JB, Fishman SJ, Alomari AI, Grant FD, Greene AK. Differential diagnosis of lower extremity enlargement in pediatric patients referred with a diagnosis of lymphedema. Plast Reconstr Surg. 2011 Apr;127(4):1571–81.

79. Bruch-Gerharz D, Gerharz C, Stege H, et al. CUtaneous vascular malformations in disappearing bone (gorham-stout) disease. JAMA. 2003 Mar 26;289(12):1479–80.

80. Al-Adnani M, Williams S, Rampling D, Ashworth M, Malone M, Sebire NJ. Histopathological reporting of paediatric cutaneous vascular anomalies in relation to proposed multidisciplinary classification system. J Clin Pathol. 2006 Dec 1;59(12):1278–82.

81. Galambos C, Nodit L. Identification of lymphatic endothelium in pediatric vascular tumors and malformations. Pediatr Dev Pathol Off J Soc Pediatr Pathol Paediatr Pathol Soc. 2005 Apr;8(2):181–9.

82. Chervenak FA, Isaacson G, Blakemore KJ, Breg WR, Hobbins JC, Berkowitz RL, et al. Fetal cystic hygroma. Cause and natural history. N Engl J Med. 1983 Oct 6;309(14):822–5.

83. Davies D, Rogers M, Lam A, Cooke-Yarborough C. Localized microcystic lymphatic malformations--ultrasound diagnosis. Pediatr Dermatol. 1999 Dec;16(6):423–9.

84. McAlvany JP, Jorizzo JL, Zanolli D, Auringer S, Prichard E, Krowchuk DP, et al. Magnetic resonance imaging in the evaluation of lymphangioma circumscriptum. Arch Dermatol. 1993 Feb;129(2):194–7.

85. Kohout MP, Hansen M, Pribaz JJ, Mulliken JB. Arteriovenous malformations of the head and neck: natural history and management. Plast Reconstr Surg. 1998 Sep;102(3):643–54.

86. Marshall ME, Hatfield ST, Hatfield DR. Arteriovenous malformation simulating Kaposi's sarcoma (pseudo-Kaposi's sarcoma). Arch Dermatol. 1985 Jan;121(1):99–101.

87. Enjolras O, Logeart I, Gelbert F, Lemarchand-Venencie F, Reizine D, Guichard JP, et al. [Arteriovenous malformations: a study of 200 cases]. Ann Dermatol Vénéréologie. 2000 Jan;127(1):17–22.

88. Ernemann U, Kramer U, Miller S, Bisdas S, Rebmann H, Breuninger H, et al. Current concepts in the classification, diagnosis and treatment of vascular anomalies. Eur J Radiol. 2010 Jul;75(1):2–11.

89. Tallman B, Tan OT, Morelli JG, Piepenbrink J, Stafford TJ, Trainor S, et al. Location of port-wine stains and the likelihood of ophthalmic and/or central nervous system complications. Pediatrics. 1991 Mar;87(3):323–7.

90. Wilson S, Venzel JM, Miller R. Angiography, gingival hyperplasia and Sturge-Weber syndrome: report of case. ASDC J Dent Child. 1986 Aug;53(4):283–6.

91. Mukhopadhyay S. Sturge-Weber syndrome: A case report. J Indian Soc Pedod Prev Dent. 2008 Jan 1;26(5):29.

92. Thomas-Sohl KA, Vaslow DF, Maria BL. Sturge-Weber syndrome: A review. Pediatr Neurol. 2004 May;30(5):303–10.

93. Pascual-Castroviejo I, Díaz-Gonzalez C, García-Melian RM, Gonzalez-Casado I, Muñoz-Hiraldo E. Sturge-Weber syndrome: study of 40 patients. Pediatr Neurol. 1993 Aug;9(4):283–8.

94. Sujansky E, Conradi S. Sturge-Weber syndrome: age of onset of seizures and glaucoma and the prognosis for affected children. J Child Neurol. 1995 Jan;10(1):49–58.

95. Sujansky E, Conradi S. Outcome of Sturge-Weber syndrome in 52 adults. Am J Med Genet. 1995 May 22;57(1):35–45.

96. Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations. J Am Acad Dermatol. 2007 Apr 1;56(4):541–64.

97. Wasenko JJ, Rosenbloom SA, Duchesneau PM, Lanzieri CF, Weinstein MA. The Sturge-Weber syndrome: comparison of MR and CT characteristics. AJNR Am J Neuroradiol. 1990 Feb;11(1):131–4.

98. RAUS I, COROIU RE, CAPUSAN CS. Neuroimaging in pediatric phakomatoses. An educational review. Clujul Med. 2016;89(1):56–64.

99. Maari C, Frieden IJ. Klippel-Trénaunay syndrome: the importance of “geographic stains” in identifying lymphatic disease and risk of complications. J Am Acad Dermatol. 2004 Sep;51(3):391–8.

100. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trénaunay syndrome: spectrum and management. Mayo Clin Proc. 1998 Jan;73(1):28–36.

101. Neubert AG, Golden MA, Rose NC. Kasabach-Merritt coagulopathy complicating Klippel-Trenaunay-Weber syndrome in pregnancy. Obstet Gynecol. 1995 May;85(5 Pt 2):831–3.

102. Viljoen D, Saxe N, Pearnj J, Beighton P. The cutaneous manifestations of the Klippel-Trenaunay-Weber syndrome. Clin Exp Dermatol. 1987 Jan 1;12(1):12–7.

103. Oduber CEU, van der Horst CMAM, Hennekam RCM. Klippel-Trenaunay syndrome: diagnostic criteria and hypothesis on etiology. Ann Plast Surg. 2008 Feb;60(2):217–23.

104. Qi HT, Wang XM, Zhang XD, Zhang MH, Li CM, Bao SG, et al. The role of colour Doppler sonography in the diagnosis of lower limb Klippel–Trénaunay syndrome. Clin Radiol. 2013 Jul;68(7):716–20.

105. Olsen NK, Zeeberg I, Jensen C. [Klippel-Trenaunay-Weber syndrome. Magnetic resonance imaging diagnosis of medullary involvement]. Ugeskr Laeger. 1989 Dec 18;151(51):3492–3.

106. Happle R. Loss of heterozygosity in human skin. J Am Acad Dermatol. 1999 Aug;41(2 Pt 1):143–64.

107. Hasegawa Y, Yasuhara M. Phakomatosis pigmentovascularis type IVa. Arch Dermatol. 1985 May;121(5):651–5.

108. Vidaurri-de la Cruz H, Tamayo-Sánchez L, Durán-McKinster C, Orozco-Covarrubias M de la L, Ruiz-Maldonado R. Phakomatosis pigmentovascularis II A and II B: clinical findings in 24 patients. J Dermatol. 2003 May;30(5):381–8.

109. Wong C-H, Tan Y-M, Chow W-C, Tan P-H, Wong W-K. Blue Rubber Bleb Nevus Syndrome: A Clinical Spectrum with Correlation Between Cutaneous and Gastrointestinal Manifestations. J Gastroenterol Hepatol. 2003 Aug 1;18(8):1000–2.

110. Jin X-L, Wang Z-H, Xiao X-B, Huang L-S, Zhao X-Y. Blue rubber bleb nevus syndrome: A case report and literature review. World J Gastroenterol WJG. 2014 Dec 7;20(45):17254–9.

111. Wong YC, Li YW, Chang MH. Gastrointestinal bleeding and paraparesis in blue rubber bleb nevus syndrome. Pediatr Radiol. 1994;24(8):600–1.

112. Jorizzo JR, Amparo EG. MR imaging of blue rubber bleb nevus syndrome. J Comput Assist Tomogr. 1986 Aug;10(4):686–8.

113. McDermott AL, Dutt SN, Chavda SV, Morgan DW. Maffucci's syndrome: clinical and radiological features of a rare condition. J Laryngol Otol. 2001 Oct;115(10):845–7.

114. Yáñez S, Val-Bernal JF, Mira C, Echevarría MA, González-Vela MC, Arce F. Spindle cell hemangioendotheliomas associated with multiple skeletal enchondromas: a variant of Maffucci's syndrome. Gen Diagn Pathol. 1998 Apr;143(5–6):331–5.

115. Boon LM, Mulliken JB, Vikkula M. RASA1: variable phenotype with capillary and arteriovenous malformations. Curr Opin Genet Dev. 2005 Jun;15(3):265–9.

116. Revencu N, Boon LM, Mendola A, Cordisco MR, Dubois J, Clapuyt P, et al. RASA1 mutations and associated phenotypes in 68 families with capillary malformation-arteriovenous malformation. Hum Mutat. 2013 Dec;34(12):1632–41.

117. Eerola I, Boon LM, Mulliken JB, Burrows PE, Dompmartin A, Watanabe S, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. Am J Hum Genet. 2003 Dec;73(6):1240–9.

118. Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, Parker VER, Blumhorst C, Darling T, et al. Clinical delineation and natural history of the *PIK3CA* -related overgrowth spectrum. Am J Med Genet A. 2014 Jul;164(7):1713–33.

119. Keppler-Noreuil KM, Rios JJ, Parker VER, Semple RK, Lindhurst MJ, Sapp JC, et al. PIK3CA-Related Overgrowth Spectrum (PROS): Diagnostic and Testing Eligibility Criteria, Differential Diagnosis, and Evaluation. Am J Med Genet A. 2015 Feb;0(2):287–95.

120. Orphanet: Rapidly involuting congenital hemangioma [Internet]. [cited 2016 Sep 22]. Available from: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=141184

121. Niu HL, Zhou SY, Lin QQ, Yi P, Wang FH, Gao Q, et al. [Clinicopathologic study of pediatric vascular anomalies: a report of 117 cases]. Zhonghua Bing Li Xue Za Zhi. 2016 Apr 8;45(4):252–7.

122. Fernández-Guarino M, Boixeda P, de Las Heras E, Aboin S, García-Millán C, Olasolo PJ. Phakomatosis pigmentovascularis: Clinical findings in 15 patients and review of the literature. J Am Acad Dermatol. 2008 Jan;58(1):88–93.

123. Nanda A, Al-Abdulrazzaq H, Habeeb YR, Zakkiriah M, Alghadhfan F, Al-Noun R, et al. Phacomatosis pigmentovascularis: Report of four new cases. Indian J Dermatol Venereol Leprol. 2016;82(3):298.

124. Deng Z-H, Xu C-D, Chen S-N. Diagnosis and treatment of blue rubber bleb nevus syndrome in children. World J Pediatr WJP. 2008 Feb;4(1):70–3.

125. Gopakumar D, Nair S. Mucocutaneous Bean syndrome: Review of literature and case report. J Indian Acad Oral Med Radiol. 2015;27(2):327.

126. Sumi Y, Taguchi N, Kaneda T. Blue rubber bleb nevus syndrome with oral hemangiomas. Oral Surg Oral Med Oral Pathol. 1991 Jan 1;71(1):84–6.

127. Dompmartin A, Ballieux F, Thibon P, et al. ELevated d-dimer level in the differential diagnosis of venous malformations. Arch Dermatol. 2009 Nov 1;145(11):1239–44.

128. Enjolras O, Ciabrini D, Mazoyer E, Laurian C, Herbreteau D. Extensive pure venous malformations in the upper or lower limb: a review of 27 cases. J Am Acad Dermatol. 1997 Feb;36(2 Pt 1):219–25.

129. Cho BC, Kim JB, Lee JW, Choi KY, Yang JD, Lee S-J, et al. Cervicofacial Lymphatic Malformations: A Retrospective Review of 40 Cases. Arch Plast Surg. 2016 Jan;43(1):10–8.

130. Dompmartin A, Vikkula M, Boon LM. Venous Malformation: update on etiopathogenesis, diagnosis & management. Phlebol Venous Forum R Soc Med. 2010;25(5):224–35.

131. Kurek KC, Luks VL, Ayturk UM, Alomari AI, Fishman SJ, Spencer SA, et al. Somatic Mosaic Activating Mutations in PIK3CA Cause CLOVES Syndrome. Am J Hum Genet. 2012 Jun 8;90(6):1108–15.

132. Alomari AI. Characterization of a distinct syndrome that associates complex truncal overgrowth, vascular, and acral anomalies: a descriptive study of 18 cases of CLOVES syndrome. Clin Dysmorphol. 2009 Jan;18(1):1–7.

133. Keppler-Noreuil KM, Rios JJ, Parker VER, Semple RK, Lindhurst MJ, Sapp JC, et al. PIK3CA-Related Overgrowth Spectrum (PROS): Diagnostic and Testing Eligibility Criteria, Differential Diagnosis, and Evaluation. Am J Med Genet A. 2015 Feb;0(2):287–95.

134. Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, Parker VE, Blumhorst C, Darling T, et al. Clinical Delineation and Natural History of the PIK3CA-Related Overgrowth Spectrum. Am J Med Genet A. 2014 Jul;164(7):1713–33.

135. Sapp JC, Turner JT, van de Kamp JM, van Dijk FS, Lowry RB, Biesecker LG. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome) in seven patients. Am J Med Genet A. 2007 Dec 15;143A(24):2944–58.

136. Chen Y, Wang B-C, Xiao Y. PI3K: A potential therapeutic target for cancer. J Cell Physiol. 2012 Jul 1;227(7):2818–21.

137. Kurek KC, Luks VL, Ayturk UM, Alomari AI, Fishman SJ, Spencer SA, et al. Somatic Mosaic Activating Mutations in PIK3CA Cause CLOVES Syndrome. Am J Hum Genet. 2012 Jun 8;90(6):1108–15.

138. Oduber CE, Young-Afat DA, Wal AC van der, Steensel MA van, Hennekam RC, Horst CM van der. The persistent embryonic vein in Klippel–Trenaunay syndrome. Vasc Med. 2013 Aug 1;18(4):185–91.

ISSVA classification for vascular anomalies ©

(Approved at the 20th ISSVA Workshop, Melbourne, April 2014)

Overview table

Vascular anomalies				
Vascular tumors	**Vascular malformations**			
	Simple	**Combined °**	**of major named vessels**	**associated with other anomalies**
Benign Locally aggressive or borderline Malignant	Capillary malformations Lymphatic malformations Venous malformations Arteriovenous malformations* Arteriovenous fistula*	CVM, CLM LVM, CLVM CAVM* CLAVM* others	See details	See list

° defined as two or more vascular malformations found in one lesion

* high-flow lesions

N.B. The classification tables do not list exhaustively all known vascular anomalies. Some rare "dermatologic" vascular anomalies will be found in dermatology textbooks.

The tumor or malformation nature or precise classification of some lesions is still unclear. These lesions appear in a separate provisional list.

Abbreviations used

For more details, click on the underlined links

Back to overview

ISSVA classification of vascular tumors ©

Benign vascular tumors
Infantile hemangioma / Hemangioma of infancy — see details
Congenital hemangioma
Rapidly involuting (RICH) *
Non-involuting (NICH)
Partially involuting (PICH)
Tufted angioma * °
Spindle-cell hemangioma
Epithelioid hemangioma
Pyogenic granuloma (aka lobular capillary hemangioma)
Others
Locally aggressive or borderline vascular tumors
Kaposiform hemangioendothelioma * °
Retiform hemangioendothelioma
Papillary intralymphatic angioendothelioma (PILA), Dabska tumor
Composite hemangioendothelioma
Kaposi sarcoma
Others
Malignant vascular tumors
Angiosarcoma
Epithelioid hemangioendothelioma
Others

* some lesions may be associated with thrombocytopenia and/or consumptive coagulopathy see details

° many experts believe that these are part of a spectrum rather than distinct entities

N.B. reactive proliferative vascular lesions are listed with benign tumors

Back to overview

ISSVA classification for vascular anomalies©

Simple vascular malformations I	
Capillary malformations (CM)	
Cutaneous and/or mucosal CM (aka “port-wine” stain)	G
CM with bone and/or soft tissue overgrowth	
CM with CNS and/or ocular anomalies (Sturge-Weber syndrome)	
CM of CM-AVM	G
CM of MICCAP (microcephaly-capillary malformation)	
CM of MCAP (megalencephaly-capillary malformation-polymicrogyria)	
Telangiectasia	
Hereditary hemorrhagic telangiectasia (HHT) (different types)	G
Others	
Cutis marmorata telangiectatica congenita (CMTC)	
Nevus simplex / Salmon patch / “angel kiss”, “stork bite”	
Others	

clic on G to see genetics

Back to overview

ISSVA classification for vascular anomalies©

Simple vascular malformations II	
Lymphatic malformations (LM)	
Common (cystic) LM	
Macrocystic LM	
Microcystic LM	
Mixed cystic LM	
Generalized lymphatic anomaly (GLA)	
LM in Gorham-Stout disease	
Channel type LM	
Primary lymphedema (different types)	G
Others	

some lesions may be associated with thrombocytopenia and/or consumptive coagulopathy see details

clic on G to see genetics

ISSVA classification for vascular anomalies©

Simple vascular malformations IIb

Primary lymphedema	
Nonne-Milroy syndrome	G
Primary hereditary lymphedema	G
Lymphedema-distichiasis	G
Hypotrichosis-lymphedema-telangiectasia	G
Primary lymphedema with myelodysplasia	G
Primary generalized lymphatic anomaly (Hennekam lymphangiectasia-lymphedema syndrome)	G
Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation syndrome	G
Lymphedema-choanal atresia	G

clic on G to see genetics

Back to overview

ISSVA classification for vascular anomalies©

Simple vascular malformations III	
Venous malformations (VM)	
Common VM	G
Familial VM cutaneo-mucosal (VMCM)	G
Blue rubber bleb nevus (Bean) syndrome VM	
Glomuvenous malformation (GVM)	G
Cerebral cavernous malformation (CCM) (different types)	G
Others	

some lesions may be associated with thrombocytopenia and/or consumptive coagulopathy see details

clic on G to see genetics

Back to overview

ISSVA classification for vascular anomalies©

Simple vascular malformations IV	
Arteriovenous malformations (AVM)	
Sporadic	
In HHT	G
In CM-AVM	G
Others	
Arteriovenous fistula (AVF) (congenital)	
Sporadic	
In HHT	G
In CM-AVM	G
Others	

Abbreviations used

clic on G to see genetics

Back to overview

ISSVA classification for vascular anomalies©

Combined vascular malformations*		
CM + VM	capillary-venous malformation	CVM
CM + LM	capillary-lymphatic malformation	CLM
CM + AVM	capillary-arteriovenous malformation	CAVM
LM + VM	lymphatic-venous malformation	LVM
CM + LM + VM	capillary-lymphatic-venous malformation	CLVM
CM + LM + AVM	capillary-lymphatic-arteriovenous malformation	CLAVM
CM + VM + AVM	capillary-venous-arteriovenous malformation	CVAVM
CM + LM + VM + AVM	capillary-lymphatic-venous-arteriovenous m.	CLVAVM

* defined as two or more vascular malformations found in one lesion

Abbreviations used

Back to overview

ISSVA classification for vascular anomalies©

Anomalies of major named vessels

(aka "channel type" or "truncal" vascular malformations)

Affect

- lymphatics
- veins
- arteries

Anomalies of

- origin
- course
- number
- length
- diameter (aplasia, hypoplasia, stenosis, ectasia / aneurysm)
- valves
- communication (AVF)
- persistence (of embryonal vessel)

Abbreviations used

Back to overview

ISSVA classification for vascular anomalies©

Vascular malformations associated with other anomalies		
Klippel-Trenaunay syndrome:	CM + VM +/- LM + limb overgrowth	
Parkes Weber syndrome:	CM + AVF + limb overgrowth	G
Servelle-Martorell syndrome:	limb VM + bone undergrowth	
Sturge-Weber syndrome:	facial + leptomeningeal CM + eye anomalies +/- bone and/or soft tissue overgrowth	G
Limb CM + congenital non-progressive limb hypertrophy		
Maffucci syndrome:	VM +/- spindle-cell hemangioma + enchondroma	
Macrocephaly - CM (M-CM / MCAP)		G
Microcephaly - CM (MICCAP)		G
CLOVES syndrome:	LM + VM + CM +/- AVM + lipomatous overgrowth	G
Proteus syndrome:	CM, VM and/or LM + asymmetrical somatic overgrowth	G
Bannayan-Riley-Ruvalcaba sd:	AVM + VM +macrocephaly, lipomatous overgrowth	G

Abbreviations used

clic on G to see genetics

Back to overview

ISSVA classification for vascular anomalies©

Provisionally unclassified vascular anomalies	
Verrucous hemangioma	
Angiokeratoma	
Multifocal lymphangioendotheliomatosis with thrombocytopenia / cutaneovisceral angiomatosis with thrombocytopenia (MLT/CAT)	
Kaposiform lymphangiomatosis (KLA)	
PTEN (type) hamartoma of soft tissue / "angiomatosis" of soft tissue	G

some lesions may be associated with thrombocytopenia and/or consumptive coagulopathy see details

clic on G to see genetics

Back to overview

ISSVA

Appendix 1
abbreviations used
(excluding gene names)

Back

AVF	arteriovenous fistula
AVM	arteriovenous malformation
CAT	cutaneovisceral angiomatosis with thrombocytopenia
CAVM	capillary arteriovenous malformation
CCM	cerebral cavernous malformation
CLAVM	capillary lymphatic arteriovenous malformation
CLOVES	congenital lipomatous overgrowth, vascular malformations, epidermal nevi, skeletal/scoliosis and spinal abnormalities
CLM	capillary lymphatic malformation
CLVAVM	capillary lymphatic venous arteriovenous malformation
CLVM	capillary lymphatic venous malformation
CM	capillary malformation
CM-AVM	capillary malformation-arteriovenous malformation
CMTC	cutis marmorata telangiectatica congenita
CNS	central nervous system
CVAVM	capillary venous arteriovenous malformation
CVM	capillary venous malformation
DIC	disseminated intravascular coagulopathy
GLA	generalized lymphatic anomaly
GSD	Gorham-Stout disease
GVM	glomuvenous malformation
HHT	hereditary hemorrhagic telangiectasia

HI	hemangioma of infancy / infantile hemangioma
IH	infantile hemangioma / hemangioma of infancy
INR	international normalized ratio
JPHT	juvenile polyposis hemorrhagic telangiectasia
KHE	kaposiform hemangioendothelioma
KLA	kaposiform lymphangiomatosis
KMP	Kasabach-Merritt phenomenon,
LM	lymphatic malformation
LVM	lymphatic venous malformation
MCAP	megalencephaly-capillary malformation-polymicrogyria
M-CM	macrocephaly-capillary malformation
MICCAP	microcephaly-capillary malformation
MLT	Multifocal lymphangioendotheliomatosis with thrombocytopenia
NICH	non-involuting congenital hemangioma
PHACE	posterior fossa malformations, hemangioma, arterial anomalies, cardiovascular anomalies, eye anomalies
PILA	papillary intralymphatic angioendothelioma
PICH	partially involuting congenital hemangioma
RICH	rapidly involuting congenital hemangioma
TA	tufted angioma
VM	venous malformation
VMCM	venous malformation cutaneo mucosal

Back to overview

ISSVA

Appendix 2-a
causal genes of vascular anomalies

Back

Capillary malformations (CM)	
Cutaneous and/or mucosal CM (aka “port-wine” stain)	GNAQ
CM with bone and/or soft tissue hyperplasia	
CM with CNS and/or ocular anomalies (Sturge-Weber syndrome)	GNAQ
CM of CM-AVM	RASA1
Telangiectasia	
Hereditary hemorrhagic telangiectasia (HHT)	
HHT1	ENG
HHT2	ACVRL1
HHT3	
JPHT (juvenile polyposis hemorrhagic telangiectasia)	SMAD4
Others	
Cutis marmorata telangiectatica congenita (CMTC)	
Nevus simplex / Salmon patch	
Others	

Back to overview

ISSVA

Appendix 2-b
causal genes of vascular anomalies

Back

Lymphatic malformations (LM)	
Primary lymphedema	
Nonne-Milroy syndrome	FLT4 / VEGFR3
Primary hereditary lymphedema	VEGFC
Primary hereditary lymphedema	GJC2 / Connexin 47
Lymphedema-distichiasis	FOXC2
Hypotrichosis-lymphedema-telangiectasia	SOX18
Primary lymphedema with myelodysplasia	GATA2
Primary generalized lymphatic anomaly (Hennekam lymphangiectasia-lymphedema syndrome)	CCBE1
Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation syndrome	KIF11
Lymphedema-choanal atresia	PTPN14

Back to overview

ISSVA

Appendix 2-c
causal genes of vascular anomalies

Back

Venous malformations (VM)	
Common VM	TIE2 somatic
Familial VM cutaneo-mucosal (VMCM)	TIE2
Blue rubber bleb nevus (Bean) syndrome VM	
Glomuvenous malformation (VM with glomus cells)	Glomulin
Cerebral cavernous malformation (CCM)	
CCM1	KRIT1
CCM2	Malcavernin
CCM3	PDCD10

Back to overview

ISSVA

Appendix 2-d
causal genes of vascular anomalies

Back

Arteriovenous malformations (AVM)	
Sporadic	
In HHT	
HHT1	ENG
HHT2	ACVRL1
JPHT (juvenile polyposis hem. telangiect.)	SMAD4
In CM-AVM	RASA1
Arteriovenous fistulas (AVF)	
Sporadic	
In HHT	
HHT1	ENG
HHT2	ACVRL1
JPHT (juvenile polyposis hemorrhagic telangiectasia)	SMAD4
In CM-AVM	RASA1

Abbreviations used

Back to overview

ISSVA

Back

Appendix 2-e
causal genes of vascular anomalies

Vascular malformations associated with other anomalies	
Klippel-Trenaunay syndrome	
Parkes Weber syndrome	RASA1
Servelle-Martorell syndrome	
Sturge-Weber syndrome	GNAQ
Limb CM + congenital non-progressive limb overgrowth	
Maffucci syndrome	
Macrocephaly - CM (M-CM or MCAP)	PIK3CA
Microcephaly - CM (MICCAP)	STAMBP
CLOVES syndrome	PIK3CA
Proteus syndrome	AKT1
Bannayan-Riley-Ruvalcaba syndrome	PTEN

Abbreviations used

Back to overview

ISSVA

Appendix 2 -f
causal genes of vascular anomalies

Back

Provisionally unclassified vascular anomalies	
Verrucous hemangioma	
Multifocal lymphangioendotheliomatosis with thrombocytopenia / cutaneovisceral angiomatosis with thrombocytopenia (MLT/CAT)	
Kaposiform lymphangiomatosis (KLA)	
PTEN (type) hamartoma of soft tissue / "angiomatosis" of soft tissue	PTEN

some lesions may be associated with thrombocytopenia and/or consumptive coagulopathy see details

Back to overview

ISSVA

Appendix 3
infantile hemangioma

Back

Pattern
- focal - multifocal - segmental - indeterminate

Different types
- superficial - deep - mixed (superficial + deep) - reticular / abortive / minimal growth - others

Association with other lesions	
PHACE association / syndrome	Posterior fossa malformations, Hemangioma, Arterial anomalies, Cardiovascular anomalies, Eye anomalies, sternal clefting and/or supraumbilical raphe
LUMBAR (SACRAL, PELVIS) association / syndrome	Lower body hemangioma, Urogenital anomalies, Ulceration, Myelopathy, Bony deformities, Anorectal malformations, Arterial anomalies, and Renal anomalies

Back to overview

ISSVA

Appendix 4
vascular anomalies
possibly associated with platelet count / coagulation disorders

Back

Anomalies	Hematological disorders
Tufted angioma Kaposiform hemangioendothelioma	Profound and sustained thrombocytopenia with profound hypofibrinogenemia, consumptive coagulopathy and elevated D-dimer (Kasabach-Merritt phenomenon)
Rapidly involuting congenital hemangioma	Transient mild/moderate thrombocytopenia, +/- consumptive coagulopathy and elevated D-dimer
Venous malformations / Lymphatic-venous malformations	Chronic localized intravascular coagulopathy with elevated D-dimer, +/- hypofibrinogenemia, and +/- moderate thrombocytopenia (may progress to DIC after trauma or operation)
Lymphatic malformations	Chronic localized intravascular coagulopathy with elevated D-dimer and +/- mild to moderate thrombocytopenia *(consider Kaposiform lymphangiomatosis)* (may progress to DIC after trauma or operation)
Multifocal lymphangioendotheliomatosis with thrombocytopenia / Cutaneovisceral angiomatosis with thrombocytopenia	Sustained, fluctuating, moderate to profound thrombocytopenia with gastrointestinal tract bleeding or pulmonary hemorrhage
Kaposiform lymphangiomatosis	Mild to Moderate thrombocytopenia, +/- hypofibrinogenemia, and D-dimer elevation

ANNEXURE- I(B)

Diagnostic Criteria: PHACE Syndrome

PHACE Syndrome

Facial Hemangioma
>5cm in diameter

PLUS

1 Major Criteria OR 2
Minor Criteria

Possible PHACE Syndrome

Facial Hemangioma >5 cm in diameter	Hemangioma of the Neck or Upper Torso	No Hemangioma
PLUS	PLUS	PLUS
1 Minor Criteria	1 Major Criteria OR 2 Minor Criteria	2 Major Criteria

Organ System	Major Criteria	Minor Criteria
Cerebrovascular	Anomaly of major cerebral arteries	Persistent embryonic artery other than trigeminal artery
	Dysplasia[a] of the large cerebral arteries[b]	Proatlantal intersegmental artery (types 1 and 2)
	Arterial stenosis or occlusion with or without moyamoya collaterals	Primitive hypoglossal artery
	Absence or moderate to severe hypoplasia of the large cerebral arteries	Primitive otic artery[c]
	Aberrant origin or course of the large cerebral arteries[b]	
	Persistent trigeminal artery	
	Saccular aneurysms of any cerebral arteries	
Structural brain	Posterior fossa anomaly	Enhancing extra-axial lesion with features consistent with intracranial hemangioma[c]
	Dandy-Walker complex or unilateral/bilateral cerebellar hypoplasia/dysplasia	Midline anomaly[d]
		Neuronal migration disorder[e]

Organ System	Major Criteria	Minor Criteria
Cardiovascular	Aortic arch anomaly	Ventricular septal defect
	Coarctation of aorta Dysplasia[a]	Right aortic arch (double aortic arch)
	Aneurysm	
		Aberrant origin of the subclavian artery with or without a vascular ring
Ocular	Posterior segment abnormality	Anterior segment abnormality
	Persistent fetal vasculature (persistent hyperplastic primary vitreous)	Sclerocornea
	Retinal vascular anomalies	Cataract
	Morning Glory disc anomaly	Coloboma
	Optic nerve hypoplasia	
	Peripapillary staphyloma	Microphthalmia
	Coloboma	
Ventral or midline	Sternal Defect	Hypopituitarism
	Sternal cleft	Ectopic thyroid
	Supraumbilical raphe	
	Sternal defects	

a) Includes kinking, looping, tortuosity, and/or dolichoectasia.
b) Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system.
c) See Structural Brain Anomalies section for discussion.
d) Callosal agenesis or dysgenesis, septum pellucidum agenesis, pituitary malformation, or pituitary ectopia.
e) Polymicrogyria, cortical dysplasia, or gray matter heterotopia.

ANNEXURE- I(C)

Classification of PPV:

In 1985, Hasegawa and Yasuhara, classified them into four types as follows:

Type 1 - PWS with epidermal nevus

Type 2 - PWS with aberrant mongolian spots (dermal melanocytosis)

Type 3 - PWS with nevus spilus

Type 4 - PWS with nevus spilus and aberrant mongolian spots .

They further divided each type into two subtypes as

a- Only cutaneous involvement

b- With systemic disease

In 2003, fifth type was added to this classification

Type 5 - Cutis marmorata telangiectatica congenita with aberrant mongolian spots

Happle classification of PPV

In 2005, Happle reclassified PPV in order to simplify the existing classification

1) Phacomatosis cesioflammea – Nevus flammeus with dermal melanocytosis
2) Phacomatosis spilorosea- Nevus rosea with nevus spilus
3) Phacomatosis cesiomarmorata- CMTC with dermal melanocytosis
4) Unclassifiable forms

ANNEXURE- I(D)

Clinical Diagnostic Criteria for PIK3CA-Related Overgrowth Spectrum (PROS)

Required: Presence of somatic *PIK3CA* mutation*
Congenital or Early Childhood Onset
Overgrowth Sporadic and Mosaic (Other terms: Patchy, Irregular)
Features as described in either A or B

A. Spectrum (two or more features)**
Overgrowth: Adipose, Muscle, Nerve, Skeletal
Vascular Malformations: Capillary, Venous, Arteriovenous Malformation, Lymphatic
Epidermal Nevus

B. Isolated features
Large Isolated Lymphatic Malformation
Isolated Macrodactyly*** OR Overgrown Splayed Feet/ Hands, Overgrown Limbs
Truncal Adipose Overgrowth
Hemimegalencephaly (bilateral)/ Dysplastic Megalencephaly/ Focal Cortical Dysplasia
Epidermal nevus
Seborrheic Keratoses
Benign Lichenoid Keratoses

Abbreviations: + present; − absent; HC hydrocephalus; ID intellectual disability

*If no mutation identified, then consider as presumptive PROS

**Typically Progressive. Can manifest as: Scoliosis (Kyphosis), Limb overgrowth, CNS (HC, Cerebellar tonsillar ectopia, Chiari, Megalencephaly, Mega corpus callosum, Regional lipomatous undergrowth with overgrowth, Infiltrating lipomatosis, Wilms tumor/ovarian cystadenoma

***Other terms: macrodystrophia lipomatosa, macrodactylia fibrolipomatosis and gigantism

ANNEXURE II

Patient Information sheet

Study Title: Descriptive study of clinical features of cutaneous vascular anomalies and associated overgrowth syndromes

Study title(for lay public): Study of blood vessel abnormalities of skin.

We are inviting you to take part in a research study. Before you decide it is important for you to understand why we are doing the research and what it will involve. Please read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you want more information. Take time to decide whether you wish to take part or not .

Purpose of research:

We are going to do a study on blood vessel abnormalities occurring in skin. There are different varieties in blood vessel abnormalities of skin. They can occur in different shapes, sizes, colours and locations. We want to do research on this topic because there is little information on this in India. This study will provide data on this topic and helps for better understanding of different types of blood vessel abnormalities occurring in skin. This will be useful for optimum management of such conditions.

Expected duration of the Subject's participation:

You will be examined by the doctor only once in the study period.

Description of the procedures:

The doctor will do detailed examination and note down the information in a special form. Relevant blood investigations which includes hemoglobin, platelets, D-dimer, Thyroid function tests will be done depending on the clinical diagnosis and extent of disease. Radiological investigations like X rays,ultrasound examination, Doppler studies, MRI will be done wherever necessary. At the end of the study, we will analyse all the data obtained so far.

Risks or discomforts to the Subject:

Small amount of blood will be collected from peripheral vein. Possible complications include

Pain

Bleeding at the puncture site

There is also a slight possibility of blood clot under skin.

We are not doing any additional tests apart from the standard protocol

Benefits to the Subject:

We are going to study the features of the disease and do tests like X rays, Ultrasound, Doppler, MRI depending on location and type of abnormality. In this study we are going to know the presence of abnormality not only in the skin but also in other organ systems which will be helpful in making a decision regarding treatment and the way in which the disease affects you.

Benefits to others:

Overall data about blood vessel abnormalities of skin isvery little in India. This study will provide data on this topic and helps for better understanding of different types of blood vessel abnormalities occurring in skin. This will be useful for optimum management of such conditions.

Confidentiality:

Your name and address will not be revealed at any point of time. All information which is collected about you during the course of the research will be kept strictly confidential unless we are required by law to share any information

Participation:

It is up to you to decide whether to take part or not. You are still free to withdraw from the study at any time, without giving any reason. A decision to withdraw, or a decision not to take part, will not affect the standard of care you receive.

Contact person:

Dr. Raja Sekhar.M,
Post Graduate resident,
Department of Dermatology,
Christian Medical College and Hospital,
Vellore.
Mobile- 9677240231
Office-04162283527

ANNEXURE -III

Informed Consent form to participate in a clinical trial

Study Title:Clinical profile of cutaneous vascular anomalies and associated overgrowth syndromes

Study Number:
Subject's Initials: _____ Subject's Name: _____
Date of Birth / Age: _____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression of the Subject/Legally Acceptable Representative):
Signatory's Name: _____ Date: ____/____/_____

Signature of the Investigator: _____

Date: ____/____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: ____/____/_____

Name & Address of the Witness: _____

ANNEXURE- IV

PROFORMA FOR VASCULAR ANOMALIES AND OVERGROWTH SYNDROMES

Date
Sl.No/CHNo

Informant

Name

Age/Sex

Address

Consanguinity

Pedigree analysis

Type of lesion- red macule/ red plaque/cutis marmorata like/ecchymotic/ clear vesicles/ bluish lesions/overgrowth

Present at birth- yes/no

If no- age of onset-

Course of lesion- stable/ progressing(rapid/proportionate), involuting

Relationship to crying (facial lesions)- Nil/prominent

Complications- Nil/ulceration/thrombosis/bleeding/infection

Exacerbating factors- Nil/trauma/infection/puberty/pregnancy

Eye-Glaucoma/blindness/coloboma

CNS-seizures/developmental delay/stroke

CVS anomalies- No/yes

Maternal antenatal & perinatal history- Infections/drugs/chorionic villus sampling/PROM/preterm delivery

FTNVD/LSCS

Birth weight

Family history/Relation

On Examination:

Type of lesion-Vascular tumour/Vascular malformation/Overgrowth

Signs- nil/Compressibility/increased local temperature/pulsatile

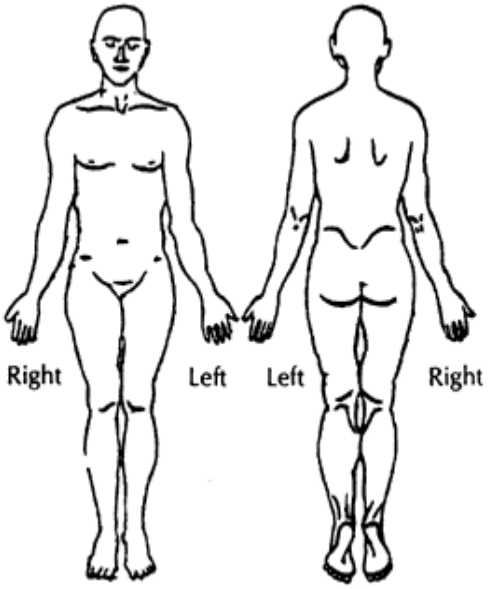
Other cutaneous lesions- lipomas/epidermal nevi/Melanocytic nevi/Dermal melanocytic lesions

Mucosa-

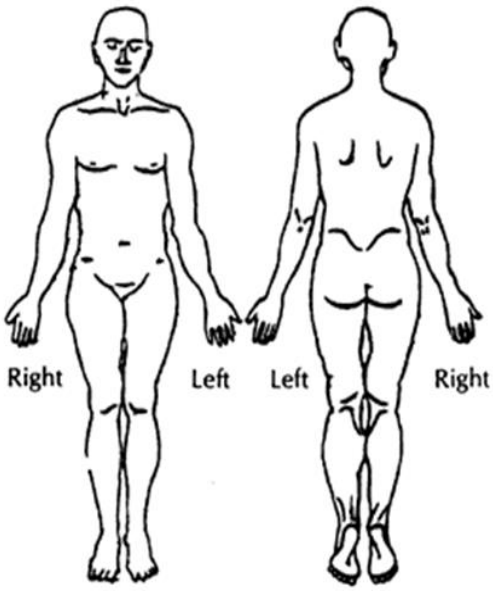
Nail-

Scalp/hair-

Body chart at onset



Body chart at present



At onset	At present
Size	Size
Colour	Colour
Texture	Texture

Features	Symptoms	Findings
Dysmorphic features CNS Eye Skeletal Spine Upper limb Lower limb Abdomen (Hepatoslenomegaly) CVS		

Investigations:

Hb

Platelets

D-dimer

X-rays

Ultrasound

Doppler

MRI

Skin biopsy

Final diagnosis

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

December 01, 2014

Dr. Raja Sekhar. M
PG Registrar
Department of Dermatology, Venereology, and Leprosy
Christian Medical College, Vellore 632 004

Sub: **Fluid Research Grant Project:**
Clinical profile of cutaneous vascular anomalies and associated overgrowth syndromes.
Dr. Raja Sekhar. M, PG Registrar, Dr. Renu George, Dr. Lydia Mathew, Dermatology, Venereology, and Leprosy, Dr. Sunil Agarwal, Vascular Surgery, Dr. Shyamkumar N Keshava, Dr. Vinu Moses, Radiology, Dr. Visalakshi, Biostatistics, CMC, Vellore.

Ref: IRB Min No: 9082 [OBSERVE] dated 06.10.2014

Dear Dr. Raja Sekhar. M,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc. Dr. Renu George, Dermatology, Venereology, and Leprosy, CMC, Vellore.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

December 01, 2014

Dr. Raja Sekhar. M
PG Registrar
Department of Dermatology, Venereology, and Leprosy
Christian Medical College, Vellore 632 004

Sub: **Fluid Research Grant Project:**
Clinical profile of cutaneous vascular anomalies and associated overgrowth syndromes.
Dr. Raja Sekhar. M, PG Registrar, Dr. Renu George, Dr. Lydia Mathew, Dermatology, Venereology, and Leprosy, Dr. Sunil Agarwal, Vascular Surgery, Dr. Shyamkumar N Keshava, Dr. Vinu Moses, Radiology,
Dr. Visalakshi, Biostatistics, CMC, Vellore.

Ref: IRB Min No: 9082 [OBSERVE] dated 06.10.2014

Dear Dr. Raja Sekhar. M,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Clinical profile of cutaneous vascular anomalies and associated overgrowth syndromes." on October 6th 2014.

The Committees reviewed the following documents:

1. IRB Application format
2. Proforma
3. Patient Information Sheet and Informed Consent Form (English, Tamil, Hindi, Telugu, Malayalam, Bengali)
4. Cv's of Drs. Raja Sekhar , Renu George, Lydia Mathew, Sunil Agarwal, Shyamkumar N Keshava, Vinu Moses, Visalakshi
5. No of documents 1-4

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on October 6th 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMC.	Internal, Clinician
Dr. Vivek Mathew	MD (Gen. Med.) D.M (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Dr. Simon Pavamani	MBBS, MD,	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Dept of Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Jacob John	MBBS, MD	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. T. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay Person
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMC, Vellore	Internal, Legal Expert

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Dr. Anuradha Rose	MBBS, MD	Assistant Professor, Community Health, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Mrs. Sheela Durai	MSc Nursing	Addl. Deputy Nursing Superintendent, Professor of Nursing in Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Mr. C. Sampath	BSc, BL	Legal Expert, Vellore	External, Legal Expert
Dr. Shirley David	M.Sc, PhD	Professor, Head of Fundamentals Nursing Department, CMC, Vellore	Internal, Nurse
Dr. Nihal Thomas	MD, MNAMS, DNB(Endo), FRACP (Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. Additional Vice Principal (Research), Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Fluid Grant Allocation:

A sum of 72,300/- INR (Rupees Seventy Two Thousand Three Hundred only) will be granted for 2 years.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg).
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc. Dr. Renu George, Dermatology, Venereology, and Leprosy, CMC, Vellore.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002.
Tel : 0416 - 2284294, 2284202 Fax : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

Child Assent Form

Title of the study: **Clinical profile of cutaneous vascular anomalies and associated overgrowth syndromes**

Protocol number:

Principal investigator: Dr.Raja Sekhar.M

Address: Department of Dermatology, Venereology and Leprosy Unit 1, Christian Medical College and Hospital (CMCH), Vellore. Phone no: 0416-2283527

Location where the study will be conducted: Department of Dermatology, Venereology and Leprosy Unit-1, CMCH.

We want to tell you about a research we are doing. A research study is a special way of finding out more about a disease. We are going to do a study on blood vessel abnormalities occurring in skin . This study will provide data on this topic and helps for better understanding of different types of blood vessel abnormalities occurring in skin. You are being asked to join the study because we feel that you could be an ideal subject for the condition being studied.

The doctor will examine your skin thoroughly and take down the details in a special proforma. If felt necessary he would click photographs of the skin lesions. For a special testing, a biopsy of the skin, where we remove a small bit of skin, may be required.

Can anything bad happen to me?

We want to tell you about some things that might hurt or upset you if you are in this study. Small amount of blood will be collected from peripheral vein. Possible complications include

- Pain
- Bleeding at the puncture site
- There is also a slight possibility of blood clot under skin

Can anything good happen to me?

In this study we are going to know the presence of abnormality not only in the skin but also in other organ systems which will be helpful in making a decision regarding treatment and the way in which the disease affects you. .

Will anyone know I am in the study?

We will not tell anyone that you took part in this study. When the study is completed, we will write a report about what we find out. We won't use your name in the report.

What happens if I get hurt?

There is a negligible risk of getting hurt. Your parents/ guardians have been informed about the same and to seek urgent medical attention as soon as possible in case of any eventuality

What if I do not want to do this?
You don't have to be in this study. It is entirely your wish. If you agree now, but refuse later, that is okay too. All you need to do is to tell us.

If you want to participate in this study, please sign below –
[ ] Yes, I want to be a part of this study
[ ] No, I do not want to be a part of this study

Name of the child:
Signature/ thumb impression of the child:
Date:

Witness mediator
Name:
Signature/thumb impression:
Date:

Person obtaining Assent:
I have explained the research at a level that is understandable by the child and believe that the child understands what is expected during the study.
Name of the investigator:
Signature:
Date:

Witness mediator
Name:
Signature:
Date:

Master chart

sno	age	sex	info	addr	consan	degree	rmac	purpap	rplaq	cmlike	ecchy	clves	bluish	og	birth	onset	course	crying	compli	othercomp	exfacto	eyesyn	cnssym	cvssym	matern	preterm	deliver
1	5	2	3	1	2		2	2	1	2	2	2	1	2	1		3	1	1		1	1	1	1	1	2	1
2	26	1	1	1	2		1	2	1	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1
3	33	1	1	1	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1
4	2.03	2	2	1	2		2	2	1	2	2	2	2	2	2	0.07	4	1	2	nasal septal resc	1	1	2	1	1	2	2
5	0.05	1	2	2	1	2	2	2	1	2	2	2	2	2	2	1.15	2	1	1		1	1	1	1	1	2	1
6	3	1	2	1	1	3	2	1	2	2	2	2	1	2	2	24	2	1	4		1	1	1	1	1	2	1
7	0.02	2	2	2	1	3	2	2	1	2	2	2	2	2	2	0.15	2	1	1		1	1	1	1	1	2	1
8	7	1	3	1	2		2	2	2	2	2	2	1	2	2	48	3	1	1		1	1	1	1			
9	73	1	1	1	2		2	1	2	2	2	1	2	2	2	864	2	1	5		1	1	1	1	1	2	1
10	26	1	1	1	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1
11	1	2	2	1	2		2	2	1	2	2	2	2	2	2	2	2	1	1		1	1	1	1	1	2	2
12	12	1	3	1	2		2	2	2	2	2	1	2	2	1		3	1	4	oozing	1	1	1	1	1	2	1
13	21	1	1	2	2		1	2	2	2	2	2	2	1	1		3	1	1		4	1	1	1	1	2	2
14	42	1	1	1	2		2	2	1	2	2	2	2	2	1		3	1	1		1	1	1	1	1	2	1
15	1	1	2	1	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	2	1	1	2	2
16	29	1	1	1	2		2	2	2	2	2	2	1	2	1		2	1	4		4	1	1	1	1	2	1
17	6	1	3	1	2		2	1	1	2	2	2	1	2	2	48	2	1	4		1	1	1	1	1	2	1
18	3	1	2	1	2		2	2	2	2	2	2	1	2	1		1	1	1		1	1	1	1	1	2	2
19	7	2	3	2	1	3	1	2	2	2	2	2	2	1	2	42	2	1	1		1	1	1	1	1	2	2
20	23	2	1	1	2		2	2	2	2	2	2	2	2	2	180	3	1	5	infection	1	1	1	1	1	2	1
22	25	1	1	1	2		1	2	2	2	2	2	2	2	1		3	1	1		1	1	1	1	1	2	1
23	61	1	1	1	2		2	2	1	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1
24	39	1	1	1	2		1	2	2	2	2	2	2	1	1		3	1	4		1	1	1	1	1	2	1
25	0.01	2	2	2	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1
26	0.1	2	2	1	2		2	2	1	2	2	2	2	2	2	0.01	2	1	1		1	1	1	1	1	2	2
27	53	1	1	1	2		1	2	2	2	2	2	2	2	1		3	1	1		1	1	1	1	1	2	1
28	45	1	1	1	2		2	2	2	2	2	2	1	2	2	480	2	1	4		1	1	1	1	1	2	1
29	0.08	2	2	2	2		2	2	1	2	2	2	2	2	2	0.15	2	1	2	bleeding, infecti	1	1	1	1	1	1	2
30	0.09	1	2	2	2		1	2	2	2	2	2	2	2	1		3	1	1		1	1	1	1	1	2	1
31	8	2	2	1	2		2	2	1	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	2
32	0.04	2	3	2	2		2	2	2	2	1	2	2	2	2	1	2	1	1		1	1	1	1	1	2	1
33	1.03	2	2	2	1	3	2	2	1	2	2	2	2	2	1		4	1	1		1	1	1	1	1	2	1
34	0.07	2	2	1	2		2	2	1	2	2	2	2	2	2	0.2	2	1	1		1	1	1	1	1	2	2
35	48	2	1	1	2		1	1	2	2	2	2	2	2	2	48	2	1	4		2	1	1	1	1	2	1
36	0.06	2	3	2	2		2	2	1	2	2	2	2	2	2	0.2	2	1	1		1	1	1	1	1	2	1
37	7	2	3	2	2		1	1	2	2	2	1	2	1	1		2	1	4		1	1	1	1	1	2	2
38	0.02	2	2	2	2		2	2	1	2	2	2	2	2	2	0.07	2	1	1		1	1	1	1	1	1	1
39	0.03	2	2	2	2		2	2	1	2	2	2	2	2	2	0.03	2	1	1		1	1	1	1	1	2	1
40	7	2	2	3	2		2	2	2	2	2	1	1	2	1		2	1	4		1	1	1	1	1	2	2
41	0.07	2	2	1	2		1	1	2	2	2	2	2	1	1		3	1	1		1	1	1	1	1	2	2
42	0.1	2	2	1	2		2	2	1	2	2	2	2	2	2	0.14	2	1	4		1	1	1	1	1	2	2
43	24	1	1	2	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1
44	17	2	1	3	2		2	2	2	2	2	1	2	2	2	36	3	1	4		4	1	1	1	1	2	1
45	0.03	2	3	2	2		2	2	1	2	2	2	2	2	2	0.1	2	1	1		1	1	1	1	1	2	1
46	7	2	2	1	2		1	2	2	2	2	2	2	2	2	36	4	1	1		1	1	1	1	1	1	2
47	56	1	1	1	2		2	2	1	2	2	2	2	2	1		3	1	4		4	3	1	1	1	2	1
48	1.03	1	3	2	2		2	2	2	1	2	2	2	1	1		3	1	1		1	1	1	1	1	2	1
49	0.01	2	2	2	2		2	2	2	1	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1
50	2.08	1	2	2	2		2	2	2	2	2	1	2	2	1		3	1	1		1	1	1	1	1	2	1
51	33	2	1	1	2		1	2	2	2	2	2	2	2	2	240	1	1	1		5	1	1	1	1	2	1
52	1.07	2	2	1	1	3	2	2	1	2	2	2	2	2	2	0.21	2	1	4		1	1	1	1	1	2	2
53	68	1	1	2	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1
54	0.02	1	2	2	2		2	2	1	2	2	2	2	2	2	0.14	2	1	2		1	1	1	1	1	2	2
55	11	2	3	3	2		2	2	1	2	2	2	2	2	2	6	4	1	1		1	1	1	1	1	2	2
56	3	1	3	1	2		2	2	2	2	2	2	1	2	2	24	2	1	1		1	1	1	1	1	2	1
57	7	1	3	3	1	2	2	2	1	2	2	2	1	1	1		2	1	4	infection	1	1	1	1	1	2	1
58	7	1	2	1	2		2	2	2	2	2	1	2	2	2	36	1	1	4		1	1	1	1	1	2	1
59	9	1	3	2	2		1	2	2	2	2	2	2	1	1		1	1	1		1	2	1	1	1	2	1
60	11	1	3	3	2		2	2	2	2	2	1	1	1	2	42	2	1	4	oozing	1	1	1	1	1	2	1
61	3.06	2	2	1	2		2	2	1	2	2	2	2	2	2	0.08	4	1	2	bleeding, infecti	1	1	1	1	1	2	1
62	6	1	3	3	2		1	2	2	2	2	2	1	2	1		3	1	4		1	1	1	1	1	2	2
631		1	2	2	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	2
64	5	2	1	3	2		1	2	2	2	2	2	1	2	1		3	1	1		1	1	1	1	1	2	1
65	8	2	3	1	2		2	2	2	2	2	2	1	2	1		2	1	1		1	1	1	1	1	2	1
66	24	2	1	1	2		2	2	2	2	2	2	1	2	1		3	1	1		1	1	1	1	1	2	1
67	0.04	2	2	2	2		2	2	1	2	2	2	2	2	1		3	1	1		1	1	1	1	1	2	1
69	1	2	2	2	1	3	2	2	1	2	2	2	2	2	1		2	1	2	bleeding, infecti	1	1	1	1	1	2	1
70	0.24	2	2	2	2		2	2	1	2	2	2	2	2	1		2	1	1		1	1	1	1	3	2	1
71	7	2	2	1	2		2	2	2	1	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1

birthw	lbw	fho	lestype	og1	sign	others	mucosa	mlesion	numles	site	head	ul	chest	abd	back	ll	perine	genital	buttoc	length	width	circum	rma	lma
2.5	2	2	1	2	3		2		1	right side of scalp,neck,(	1	1	1	2	2	2	2	2	2	24	20	2		
3	2	2	2	2	1		1	PWS- mucosal aspect of	1	left side of V3 segment	1	2	2	2	2	2	2	2	2	11	10	2		
3	2	2	2	2	1		2		1	pws-right upperlimb	2	1	2	2	2	2	2	2	2			2		
2.75	2	2	1	2	1	telangiectasia- face	1	nasal septum resorptior	1	nose, lips	1	2	2	2	2	2	2	2	2	2	2	2		
2.9	2	2	1	2	1		2		1	left parietal area of scal	1	2	2	2	2	2	2	2	2	6	4	2		
3	2	2	2	2	1		2		2	subcut swelling-right thi	2	2	2	2	2	1	2	2	2			1		
3.5	2	2	1	2	1		2		1	scalp	1	2	2	2	2	2	2	2	2	1	1	2		
			2				2		1	right subcostal area	2	2	2	1	2	2	2	2	2	7	4	2		
3	2	2	2	2	1		2		1	scrotum	2	2	2	2	2	2	2	1	2			2		
3	2	2	2	2	1		2		1	left side of neck	1	2	2	2	2	2	2	2	2	2	2	2		
2.3	1	2	1	2	1		2		1	left side of abdomen	2	2	2	1	2	2	2	2	2	7	3	2		
3	2	2	2	2	1		2		1	right scapula	2	2	2	2	1	2	2	2	2	5	5	2		
3.5	2	2	2	1	1	lipomatous growth- bac	2	fissured tongue	2	palms, soles, abdomen,	1	1	2	1	1	1	2	2	2					
3	2	2	2	2	1	CALM- left thigh	1	left conjuctiva	1	left V1 area	1	2	2	2	2	2	2	2	2	15	12	2		
4	2	2	2	2	1		2		1	left V1, V2	1	2	2	2	2	2	2	2	2					
3	2	2	2	2	2	nevus spilus	2		1	left mid back	2	2	2	2	1	2	2	2	2	8	7	2		
3	2	2	2	2	1		1	right side of tongue	2	tongue, upper limbs, pa	2	1	2	2	2	1	2	2	2					
2.6	2	2	2	2	2		2		1	right cheek	1	2	2	2	2	2	2	2	2			2		
3	2	2	2	1	3	red papules- right foot t	2		1	right LL	2	2	2	2	2	1	2	2	2			1		
3	2	2	2	2	1	hypertrophy of vulva-rig	1	vulva	1	vulva	2	2	2	2	2	2	2	1	2					
2.5	2	2	2	2	1	Nevus anemicus(chest,b	2		1	right LL	2	2	2	2	2	1	2	2	2					
3	2	2	2	2	1		2		1	right upperlimb	2	1	2	2	2	2	2	2	2					
	1	2	2	1	1	acroangiodermatitis- lef	2		2	lower limbs (left> right)	2	2	2	2	2	1	2	2	1					
2.4	1	2	2	2	1		2		1	right lower limb, labia m	2	2	2	2	2	1	2	1	2					
3.4	2	2	1	2	1		2		1	lower lip	1	2	2	2	2	2	2	2	2	1.5	1	2		
3	2	2	2	2	1	giant acrochordon	1	PWS- right side of soft p	1	right V2 area	1	2	2	2	2	2	2	2	2					
3	2	2	2	2	1		1	lower lip swelling	1	lower lip	1	2	2	2	2	2	2	2	2	1	1	2		
2.75	2	2	1	2	1		2		1	left upperlimb	2	1	2	2	2	2	2	2	2	20	8	2		
2.4	1	2	2	2	1		2		1	right V1, V2	1	2	2	2	2	2	2	2	2					
2.85	2	2	1	2	3		2		1	right upperlimb	2	1	2	2	2	2	2	2	2	6.5	4	2		
2.39	1	2	1	2	3		2		1	right knee	2	2	2	2	2	1	2	2	2	6	5	2		
3.2	2	2	1	2	1		2		1	left infraorbital area	1	2	2	2	2	2	2	2	2	6	5			
3.5	2	2	1	2	1	CALM- abdomen	2		1	left chest	2	2	1	2	2	2	2	2	2	7	6			
3	2	1	2	2	1		1	nasal mucosa, tongue, g	2	nasal mucosa, tongue, f	1	1	2	2	2	2	2	2	2					
2.6	2	2	1	2	1	CALM- left leg	2		1	left chest	2	2	1	2	2	2	2	2	2	2	2			
2.5	2	2	2	1	1		2		2	right lower limb	2	2	2	2	2	1	2	2	1			1		
2.84	2	2	1	2	1		2		1	scalp	1	2	2	2	2	2	2	2	2	2.5	1.5			
3.5	2	2	1	2	3		1	right conjunctiva	1	right infraorbital	1	2	2	2	2	2	2	2	2	4.5	4.2			
3	2	2	2	2	2	dark verrucous growths	2		2	right LL	2	2	2	2	2	1	2	2	2			1		
3	2	2	2	1	1		2		2	right LL	2	2	2	2	2	1	2	2	2			1		
3.3	2	2	1	2	3		1	gums,right buccal muco	1	right -face	1	2	2	2	2	2	2	2	2	10	8	2		
3	2	2	2	2	1	alopecia areata	2		2	right UL	2	1	2	2	2	2	2	2	2					
	2	2	2	2	1		2		1	right buttock	2	2	2	2	2	2	2	2	1	8.5	2	2		
		2	1	2	1		2		1	scalp	1	2	2	2	2	2	2	2	2	2	2	2		
1.7	1		2	2	1		2		1	right cheek	1	2	2	2	2	2	2	2	2	5	3	2		
3	2	2	2	2	3	nodular hyperplasia	1	right buccal mucosa, pa	1	right- face	1	2	2	2	2	2	2	2	2					
3.25	2	2	2	1	1	dilated veins	2		1	left LL	2	2	2	1	1	1	2	2	1			1		
	2	2	2	2	1		2		1	left UL	2	1	2	2	2	2	2	2	2					
3.3	2	2	2	2	1	nevus depigmentosus- r	2		1	right shoulder	2	2	2	2	1	2	2	2	2	5	4	2		
2.5	2	2	2	2	1		1	upper lip mucosa	2	right -face	1	2	2	2	2	2	2	2	2	8	6	2		
2.7	2	2	1	2	3		2		1	left periorbital	1	2	2	2	2	2	2	2	2	4	6	2		
3	2	2	2	2	1		2		1	left chest, UL	2	1	1	2	2	2	2	2	2					
3	2	2	1	2	3		1	right conjuctiva, nasal, b	1	right- face	1	2	2	2	2	2	2	2	2					
3	2	2	1	2	1		2		1	scalp	1	2	2	2	2	2	2	2	2	2	1.5	2		
3	2	2	2	2	1		2		1	left- neck	1	2	2	2	2	2	2	2	2	10	10	2		
2.5	2	1	2	1	1	verrucous growths	2		2	right UL	2	1	2	2	2	2	2	2	2					
3	2	2	2	2	1		1	urethral meatus	1	glans , urethral meatus	2	2	2	2	2	2	2	1	2					
2.25	1	1	2	1	1	Dermal melanocytosis, (	1	Melanosis oculi, blue gr	2	Disseminated- predomi	1	1	1	1	1	1	2	2	1			2		
3	2	2	2	1	2		2		2	buttocks, left LL	2	2	2	2	2	1	1	1	1			1		
2.2	1	2	1	2	1		2		1	back	2	2	2	2	1	2	2	2	2	5	3	2		
3	2	2	2	2	3		2		1	right foot	2	2	2	2	2	1	2	2	2					
3.5	2	2	2	2	1	depigmented macule-rig	2		1	glabella	1	2	2	2	2	2	2	2	2					
3	2	2	2	2	2		1	lower lip, right buccal m	1	right- face	1	2	2	2	2	2	2	2	2					
3	2	2	2	2	2		2		1	left UL	2	1	2	2	2	2	2	2	2	5	3	1		
3	2	2	2	2	4		1	tongue	1	tongue	1	2	2	2	2	2	2	2	2					
2.2	2	2	1	2	1		2		1	right LL	2	2	2	2	2	1	2	2	2	5	3	2		
2.5	2	2	1	2	3		2		1	nape of neck	1	2	2	2	2	2	2	2	2	6	6	2		
		2	1	2	1		1	upper lip	2	scalp, forehead,upper li	1	1	1	1	1	1	2	1	2					
3	2	2	2	2	1		2		1	left-trunk, UL,LL	1	1	2	2	1	1	2	2	1					

rmf	lmf	rmt	lmt	rml	lml	dysm	dysmtype	cns	eye	spine	hyper	hypo	abdomen	cvs	ddimval	ddimer	hb	platelets	tsh	usg	doppler	mri	embryonic	phleb	otherradio	biopsy	otherbiop	diag	otherdiag
						2		1	1	1	2	2	1	1	291	1	9.8	3.8		soft tissue thickening-minimal cysti		3	2	2	USG,MRI-soft tissue thickening-m			3	
						2		1	1	1	2	2	1	1														6	
						2		1	1	1	2	2	1	1			13.6	2.2	1.348									6	
						1	right eye squint, nasal s	2	2	1	2	2	1	1			13.6	3.63		usg abdomen- normal					MRI brain- ?Dandy walker malfor			1	probable PHACES syndr
						2		1	1	1	2	2	1	1														1	
		24	23			2		1	1	1	2	2	1	1	107	1	8.6			abd-normal, msk- low flow malforn		1	2	2		6	focal positivity of d2-40	8	
						2		1	1	1	2	2	1	1														1	
						2		1	1	1	2	2	1	1			10.6	1.58				2	2	2				10	
						2		1	1	1	2	2	1	1			13.1		2.916							6		8	
						2		1	1	1	2	2	1	1			14.1	2.96										6	
						2		1	1	1	2	2	1	1	1035	2	11.6	2.12	2.86	soft tissue thickening- abdomen						2		4	
						2		1	1	1	2	2	1	1						cystic lesion, low flow malformatio		1	2	2		6		8	
						1	hemihypertrophy- left t	1	1	1	1	2	1	1					5.208									11	CLOVES syndrome
						2		1	1	1	2	2	1	1											x ray skull- normal	4		6	
						2		2	1	1	2	2	1	1			12	3.8	3.837			3			leptomeningeal angiomatosis- lef			11	Sturge Weber syndrome
						2		1	1	1	2	2	1	1						elongated cystic spaces	2							10	
						2		1	1	1	2	2	1	1			11.6					1	2	1		7		11	Blue rubber bleb syndro
						2		1	1	1	2	2	1	1						compressible lesion wit	1		2	2				7	
		37	28	27	17	1	right LL hypertrophy	1	1	1	1	2	1	1	1141	2		3.24			1	1	1	2	varicose veins- right LL			11	Klippel Trenaunay syndr
						2		1	1	1	2	2	1	1			10.8	2.8				1	2	2			epitheloid granulomato	8	
						1	high arched palate, right	2	2	2	2	1	1	1			15.6	2.01	3.9	hemangioma of liver					MRI- right lumbosacral plexopath			6	
						2		1	1	1	2	2	1	1			13.3	1.63										6	
						1	left LL hypertrophy	1	1	1	1	2	1	1	253	1	12.9	1.08			1		2	2				11	Klippel-Trenaunay syndr
						2		1	1	1	2	2	1	1			16.6	2.88	16.2									6	
						2		1	1	1	2	2	1	1														1	
						2		1	1	1	2	2	1	1			13.8	1.66	1.34									6	
						2		1	1	1	2	2	1	1							2		2	2				10	
						2		1	1	1	2	2	1	1			10.3	5.43	1.319									1	
						2		1	1	1	2	2	1	1					2.558									6	
						2		1	1	1	2	2	1	1				1.93										2	
						2		1	1	1	2	2	1	1	2810	2	13.9	0.38		solid mass with arteial s	2		2	2				5	Kasabach-Merritt syndr
						2		1	1	1	2	2	1	1				5.72		ill-defined hyperechoeic lesion								1	
						2		1	1	1	2	2	1	1														1	
						2		1	1	1	2	2	1	1			9.5			fatty liver					CT thorax- no e/o AVM, pulm TE			11	HHT
						2		1	1	1	2	2	1	1														1	
		32	31	27	20	1	right LL hypertrophy	1	1	1	1	2	1	1			11.5					1	2	2	VLM-rt pelvis, LL			11	KTS
						2		1	1	1	2	2	1	1					13.01									1	
						2		1	1	1	2	2	1	1														1	
				37	33	2		1	1	1	2	2	1	1	146	1					1		1	2				9	
		24	20	24	16	1	right LL hypertrophy	1	1	1	1	2	1	1	1496	2	10	5.74			1		1	2	VLM			11	KTS
						2		1	1	1	2	2	1	1			10.4	2.5	3.33						doppler- increased vascularity			1	
						2		1	1	1	2	2	1	1			15.9											6	
						2		1	1	1	2	2	1	1								1	2	2				8	
						2		1	1	1	2	2	1	1					6.218									1	
						2		1	1	1	2	2	1	1			14.2	2.72										11	spider nevus
						2		1	2	1	2	2	1	1	187	1	13.9	1.47							doppler-right face, orbit, retromc			6	PWS with nodular hype
		21	23			1	left LL hypertrophy	1	1	1	1	2	1	1			16.3	2.33			3		1		varicose veins			11	CMTC with limb hypertr
						2		1	1	1	2	2	1	1					5.51									11	CMTC
						2		1	1	1	2	2	1	1						slow flow	1		2	2				8	
						2		1	1	1	2	2	1	1														6	
						2		1	1	1	2	2	1	1														1	
						2		1	1	1	2	2	1	1														6	
						2		2	2	1	2	2	1	1								3	2	2	dysgenesis of rt ICA, cerebellar hy			1	PHACES syndrome
						2		1	1	1	2	2	1	1			13.3		4.762		3				internal vascularity			1	
						2		1	1	1	2	2	1	1			9.7	3.4			1	1	2	2	LM- left parotid, submandibular g			8	
						2		1	1	1	2	2	1	1	369		13.5	2.73				1	2	2	thrombosis of basilic vein, intraos			7	
						2		1	1	1	2	2	1	1													6		8	
						1	Left forearm, LL hypertr	2	2	1	1	2	1	1			13.3	2.46			1	3	2	2	Foci of abnormal intens	4		11	PPV 2B, KTS, NF 1
		32	34	25	26	1	limb hypertrophy	1	1	1	2	2	1	1	705	2	5.8	2.47			1	1	2	2	multiple splenic hemang	6		9	
						2		1	1	1	2	2	1	1							3				internal vascularity			1	
						1	macrodactyly-right hallu	1	1	1	2	2	1	1	171	1	12	3.02				2			AVM with intraosseous compone			11	CM-AVM
						2		1	1	1	2	2	1	1														6	
						2		1	1	1	2	2	1	1												5		6	CM-VM
15	17					2		1	1	1	2	2	1	1				3.51		VM	1		2	2				7	
						2		1	1	1	2	2	1	1								2						10	
						2		1	1	1	2	2	1	1														2	
						2		1	1	1	2	2	1	1			8.6	5.86							echo- normal			1	
						2		1	1	1	2	2	1	1			10.9	2.38	2.868	anechoeic lesions in rt lobe of liver								11	Neonatal hemangiomat
		16	16			2		1	1	1	2	2	1	1														11	CMTC

72	1.08	2	3	1	2		2	2	1	2	2	2	2	2	2	0.1	1	1	1		1	1	1	1	1	2	2	3.4	2
73	0.06	2	2	2	2		2	2	1	2	2	2	2	2	1		1	1	2		1	1	1	1	1	2	2	3.25	2
74	1.06	2	2	2	2		1	2	2	2	2	2	2	2	1		1	1	1		1	2	1	1	1	2	2	3.25	2
75	2	2	3	1	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	2	2.8	2
76	13	2	3	2	1	3	2	2	2	2	2	1	2	2	2	36	3	1	1		1	1	1	1	1	2	1	3	2
77	5	1	3	1	2		1	2	2	2	2	2	2	1	1		3	1	1		1	1	1	1	1	2	2	3.5	2
78			2	2	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1	2.65	2
79	35	1	1	1	2		1	2	2	2	2	2	2	2	2	18	1	1	1		1	1	1	1	1	2	1	3	2
80	34	1	1	1	2		2	2	2	2	2	2	1	2	2	360	1	1	1		1	1	1	1	1	2	2	3.5	2
81	10	1	3	1	2		2	2	2	2	2	1	2	2	2	108	3	1	1		1	1	1	1	1	1	2	1.34	1
82	1.08	1	2	3	2		1	2	2	2	2	2	2	1	1		4	1	1	developmental d	1	2	2	1	1	2	1	2.5	2
83	15	2	2	2	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1	3.5	2
84	0.11	2	2	1	2		2	2	1	2	2	2	2	2	1		2	1	2	visual field obstr	1		1	1	1	2	2	2.7	2
85	0.03	1	2	2	2		2	2	1	2	2	2	2	2	2	1	2	1	1		1	1	1	1	3	2	2	2.56	2
86	0.05	1	3	2	1	2	1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	2	2.5	2
87	0.04	2	3	2	2		2	2	1	2	2	2	2	2	2	0.4	2	1	1		1	1	1	1	1	2	1	3.5	2
88	46	1	1	1	2		2	2	1	2	2	2	2	2	2	432	3	1	4		2	1	1	1	1	2	1	3	2
89	39	1	1	1	2		2	2	2	2	2	2	1	2	2	48	3	1	1		1	1	1	1	1	2	1	3	2
90	15	2	3	1	2		2	2	1	2	2	1	1	2	2	3	2	2	4		1	1	1	1	1	2	1	2.5	2
91	9	2	3	1	2		2	2	2	2	2	2	1	1	2	84	3	1	1		1	1	1	1	1	2	1	3	2
92	24	1	1	1	2		2	2	2	2	2	2	1	2	2	216	3	1	1		1	1	1	1	1	2	1		
93	36	1	1	2	1	3	1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1		
94	0.1	1	2	2	2		2	2	1	2	2	2	2	2	2	0.1	2	1	1		1	1	1	1	1	2	1	3	2
95	0.02	2	2	2	2		2	2	1	2	2	2	2	2	2	0.1	2	1	1		1	1	1	1	1	2	1	3.15	2
96	0.08	2	3	2	2		2	2	1	2	2	2	2	2	2	3	2	1	1		1	1	1	1	1	2	1	2.7	2
97	30	2	1	1	2		2	2	2	2	2	1	2	2	2	132	3	1	1	itching	1	1	1	1	1	2	1		
98	6	2	2	1	2		2	1	2	2	2	1	2	2	1		3	1	4	oozing	1	1	1	1	1	2	1	3	2
99	0.08	2	2	2	2		2	2	1	2	2	2	2	2	2	0.1	2	1	1		1	1	1	1	1	2	1	3	2
100			2	1	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	2	3	2
101	3	2	3	3	2		2	2	2	1	2	2	2	2	1		1	1	1		1	2	2	1	1	2	2	3.25	2
102	24	2	1	1	2		2	2	1	2	2	2	2	2	1		2	1	1		1	1	1	1	1	2	1	3	2
103	7	1	3	1	2		2	2	1	2	2	2	2	2	2	0.15	4	1	1		1	1	1	1	1	1	2	1.75	1
104	0.08	2	2	1	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	3	1	1	2	2	3.2	2
105	3	2	3	3	2		2	2	1	2	2	2	2	2	2	0.07	4	1	1		1	1	1	1	1	2	1		2
106	27	2	1	2	2		2	2	2	2	2	1	2	2	2	240	3	1	1		1	1	1	1	1	2	1	3	2
107	30	1	1	1	2		1	2	2	2	2	2	2	2	2	120	3	1	1		1	1	1	1	1	2	2	2.8	2
108	41	2	1	2	2		2	2	1	2	2	2	2	2	2	0.07	3	1	1		1	1	1	1	1	2	1	3	2
109	9	2	3	1	2		2	2	2	2	2	2	1	2	1		3	1	3		1	1	1	1	1	2	1	3	2
110	0.02	1	2	2	2		1	2	2	2	2	2	2	2	2	1	1	1	1		1	1	1	1	1	1	1	2.2	1
111	0.03	2	2	2	2		2	2	1	2	2	2	2	2	2	1	2	1	1		1	1	1	1	1	2	1	3.22	2
112	0.04	2	3	2	2		2	2	1	2	2	2	2	2	2	0.1	2	1	2		1	1	1	1	1	1	2	1.16	1
113	0.07	2	2	2	1	2	2	2	1	2	2	2	2	2	2	2	4	1	1		1	1	1	1	1	2	2	3	2
114	14	1	2	1	2		2	2	2	2	2	1	2	2	2	6	3	1	4		1	1	1	1	1	2	2	2.3	1
115		2	2	2	2		2	2	1	2	2	2	2	2	2	1	2	1	1		1	1	1	1	1	2	1	3.5	2
116	0.06	2	2	2	2		2	2	1	2	2	2	2	2	2	2	2	1	1		1	1	1	1	1	2	2	1.5	1
117	0.03	1	2	2	2		2	2	1	2	2	2	2	2	2	0.1	2	1	1		1	1	1	1	1	2	2	2.2	1
118	0.03	2	2	2	1	3	2	2	1	2	2	2	2	2	1		2	1	1		1	1	1	1	1	2	1		
119	0.04	1	2	2	2		2	2	1	2	2	2	2	2	2	0.2	1	1	1		1	1	1	1	1	2	1	3.3	2
120	0.08	2	2	2	2		2	2	1	2	2	2	2	2	2	2	1	1	1		1	1	1	1	1	2	2	2.75	2
121	0.1	2	2	2	2		1	2	2	2	2	2	2	1	2	3	1	1	1		1	1	1	1	1	2	1	2.8	2
122	0.06	1	2	2	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	1	1	1.9	1
123	0.01	2	2	2	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	2	3.28	2
124	8	1	3	1	2		2	2	2	2	2	2	2	2	1		3	1	2	infection	1	1	1	1	1	2	1	3.5	2
125	0.02	2	2	2	1	3	2	2	1	2	2	2	2	2	2	1	2	1	1		1	1	1	1	1	2	2	2.85	2
126	52	2	1	2	2		1	2	2	2	2	1	2	1	1		3	1	5		1	1	1	1	1	2	1	3	2
127	0.03	1	2	2	2		2	2	1	2	2	2	2	2	2	0.1	2	1	1		1	1	1	1	1	1	2	1.46	1
128	0.02	1	2	2	1	3	2	2	1	2	2	2	2	2	2	0.1	2	1	1		1	1	1	1	1	2	1	2.53	2
129	17	1	3	3	2		1	2	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	2	3	2
130	9	2	2	3	2		2	2	2	2	2	2	1	2	1		2	1	1		1	1	1	1	1	2	2	3	2
131	0.03	1	2	1	2		2	2	2	2	2	1	1	1	1		2	1	1		1	1	1	1	1	2	1	3	2
132	0.03	2	2	2	2		2	2	1	2	2	2	2	2	1		4	1	1		1	1	1	1	1	2	1	2.9	2
133	34	2	1	1	2		2	2	2	2	2	2	1	2	2	150	3	1	4	pain	1	1	1	1	1	2	1	3	2
134	29	1	1	3	2		1	1	2	2	2	2	2	2	1		1	1	1		1	1	1	1	1	2	1		
135	6	2	2	2	2		2	2	1	2	2	2	2	2	1		4	1	4		1	1	2	1	1	1	1	2.5	2
136	11	2	2	1	2		2	2	2	2	2	2	1	2	2	36	2	1	4		1	1	1	1	1	2	2	2.68	2
137	3	2	3	1	2		2	2	1	2	2	2	2	2	2	1	3	1	1		1	1	1	1	1	2	1	3	2
138	11	1	2	2	1	3	2	2	2	2	2	1	2	2	2	60	3	1	1		1	1	1	1	1	2	1	2.7	2

2	1	2	3		2		2	forehead, rt-chest	1	2	1	2	2	2	2	2	2	3.5	2	2				
2	1	2	1		2		1	back	2	2	2	2	1	2	2	2	2							
2	2	2	1	dermal melanocytosis	1	melanosis oculi, buccal	2	disseminated	1	1	2	2	1	1	2	2	2			2				
2	2	2	1	sacral dimples,mongolia	2		1	left LL	2	2	2	2	2	1	2	2	1							
2	2	2	1		2		1	left- chest	2	2	1	2	2	2	2	2	2	3	3	2				
2	2	1	1	lipomatous growth- bac	1	epidermal nevus- upper	2		1	1	2	2	1	1	2	2	1							
2	2	2	1		2		1	right LL	2	2	2	2	2	1	2	2	2							
2	2	2	1		2		1	right UL	2	1	2	2	2	2	2	2	2							
2	2	2	2		1	oral mucosa- left	1	lower lip	1	2	2	2	2	2	2	2	2	1	0.5	2				
2	2	2	1		2		1	left groin	2	2	2	2	2	2	2	2	2	1	1	2				
2	2	1	1	dermal melanocytosis	1	palate,buccal mucosa-P	2	head and neck, limbs	1	1	1	1	1	1	2	2	1							
2	2	2	1		2		2	face	1	2	2	2	2	2	2	2	2							
2	1	2	3		1	nasopharynx,larynx	1	right- face	1	2	2	2	2	2	2	2	2							
2	1	2	3	sacral dimples	1	tongue	2	tongue,abdomen, back	1	2	2	1	1	2	2	2	2	5	3	2				
2	2	2	1	arthrogryphosis	2		1	right-V2,V3	1	2	2	2	2	2	2	2	2							
2	1	2	1		2		1	left cheek	1	2	2	2	2	2	2	2	2	1.5	1.2	2				
2	2	2	1		2		1	right middle finger pulp	2	1	2	2	2	2	2	2	2	1	1	2				
2	2	2	4	acrochordon	2		1	left arm	2	1	2	2	2	2	2	2	2	7	7	2				
2	2	2	1		2		2	left upperlimb	2	1	2	2	2	2	2	2	2							
2	2	1	1	blaschoid pigmentation-	2		1	right thigh	2	2	2	2	2	1	2	2	2			1				
2	2	2	4		2		1	upper lip	1	2	2	2	2	2	2	2	2	5	2	2				
2	2	2	1	psoriasis	2		1	right arm	2	1	2	2	2	2	2	2	2							
2	1	2	1	alopecia areata	2		1	right thigh	2	2	2	2	2	1	2	2	2	5	5	2				
2	1	2	1		2		1	left UL	2	1	2	2	2	2	2	2	2	1.5	1	2				
2	1	2	1		2		2	scalp, right supraclavicu	1	2	1	2	2	2	2	2	2	1	0.5	2				
2	2	2	1		2		1	left chest	2	2	1	2	2	2	2	2	2	4	3	2				
2	2	2	1		2		2	left-neck,chest,axilla, fo	1	1	1	2	2	2	2	2	2							
2	1	2	1		2		1	right-scalp	1	2	2	2	2	2	2	2	2	1	1	2				
2	2	2	1		2		1	forehead	1	2	2	2	2	2	2	2	2							
2	2	1	1	dermal melanocytosis-le	2		2	disseminated	1	1	1	1	1	1	1	1	1			1	17	18		
2	2	2	3		2		1	left forehead	1	2	2	2	2	2	2	2	2	7	7	2				
2	1	2	1	CALM, N.depigmentosu	2		1	right forehead	1	2	2	2	2	2	2	2	2	2	1	2				
2	2	2	1		2		1	occiput	1	2	2	2	2	2	2	2	2							
2	1	2	1		2		1	left -neck	1	2	2	2	2	2	2	2	2	5	4	2				
2	2	2	1		2		1	clitoris, right labia maju	2	2	2	2	2	2	2	1	2							
2	2	2	1		2		2	left forearm	2	1	2	2	2	2	2	2	2	5	4	2				
2	2	2	1	herpes genitalis	2		2	left-face,neck,back	1	2	2	2	1	2	2	2	2	8	4	2				
2	2	2	1		2		1	right foot	2	2	2	2	2	1	2	2	2	7	3	2				
2	2	2	1		2		1	glabella	1	2	2	2	2	2	2	2	2	1	1	2				
2	1	2	1		2		1	nose	1	2	2	2	2	2	2	2	2	0.7	0.7	2				
2	1	2	1		2		1	right-scalp	1	2	2	2	2	2	2	2	2	2	2					
2	1	2	1		2		1	right- back	2	2	2	2	1	2	2	2	2	1	0.6	2				
2	2	2	1		2		1	right lower back	2	2	2	2	1	2	2	2	2	21	7	2				
2	1	2	1		2		1	scalp	1	2	2	2	2	2	2	2	2	0.7	0.7	2				
2	1	2	1		1	left-upper lip,buccal mu	1	left- face	1	2	2	2	2	2	2	2	2	6	4	2				
2	1	2	1		1	upper lip	2	upper lip,scrotum,left ri	1	1	2	2	2	2	2	1	2							
2	1	2	1		2		1	left chin	1	2	2	2	2	2	2	2	2	2.3	2.1	2				
2	1	2	1		2		1	scalp	1	2	2	2	2	2	2	2	2	1	0.5	2				
2	1	2	1		2		1	left- scalp	1	2	2	2	2	2	2	2	2	1	0.7	2				
2	2	1	1		2		1	right LL	2	2	2	2	2	1	2	2	2			1				
2	2	2	1		2		1	right wrist	2	1	2	2	2	2	2	2	2							
2	2	2	1		2		1	left UL	2	1	2	2	2	2	2	2	2							
2	2	2	1	verrucous plaques over	2		1	lower limbs	2	2	2	2	2	1	2	2	2							
2	1	2	1		1	upper lip	1	upper lip	1	2	2	2	2	2	2	2	2	2	1.5	2				
2	2	1	1	lipomatous overgrowth-	2		2	left trunk, UL	2	1	1	2	1	2	2	2	2			1	23	36	21	31
2	1	2	1		2		2	forehead,nose,neck,arm	1	1	2	2	1	1	2	2	2							
2	1	2	3		2	tongue tie	1	right wrist	2	1	2	2	2	2	2	2	2	5.5	3.5	2				
2	2	2	1	epiderma nevus-right fa	2	high arched palate, fissu	2	right palm, forearm	2	1	2	2	2	2	2	2	2			1				
2	2	2	2		2		2	right chest,axilla, UL	2	1	1	2	2	2	2	2	2				19	17	20	16
2	2	1	2		2		2	left trunk, UL	2	1	1	2	2	2	2	2	2							
2	1	2	1		2		1	buttocks	2	2	2	2	2	2	2	2	1							
2	2	2	2		2		1	left arm	2	1	2	2	2	2	2	2	2	4	3.5	2				
1	2	2	1		2		1	left trunk,UL	1	1	1	2	1	2	2	2	2							
2	1	2	1	dermal melanocyticlesio	2		1	left arm	2	1	2	2	2	2	2	2	2							
2	2	2	2	blue lunula- left index fi	2		2	left thumb,index finger	2	1	2	2	2	2	2	2	2							
2	1	2	1		2		1	right neck	1	2	2	2	2	2	2	2	2	3	1	2				
2	2	2	1		2		1	left upper thigh	2	2	2	2	2	1	2	2	2	13	7	2				

				2		1	1	1	2	2	1	1																1	
				2		1	1	1	2	2	1	1					3.49											11	
				1	macrocephaly- 52.5 cm	2	2	1	2	2	1	1								3			MRI brain-dilated tortuous vessel				11	PPV-2b with SWS
24	26			2		1	1	1	1	2	1	1						muscle hypertrophy									6	PPV type 2a
				2		1	1	1	2	2	1	1						no deep involvement									8	
				1	Lt hemihypertrophy,lipo	1	1	1	1	2	1	1			11.7	2.73	1.97	small malrotated left kidney							epidermal nevus, lipom		11	CLOVES syndrome
				2		1	1	1	2	2	1	1					7.55										6	
				2		1	1	1	2	2	1	1							3				no deeper involvement				6	
				2		1	1	1	2	2	1	1															7	
				2		1	1	1	2	2	1	1												6			8	
				1	overgrowth-rt cheek,arr	2	2	1	1	2	1	2			10.2	3.92	3.479			3			SWS(Lt >Rt), X ray-cardiomegaly				11	PPV 2b with SWS, right
				2		1	1	1	2	2	1	1			13	3.85							X ray skull- no e/o SWS				6	
				2		1	1	1	2	2	1	1											echo- normal				1	
				2		1	1	1	2	2	1	1			9.4	3.49	4.395	no internal hemangiomas, rt kidney not visualised									1	multiple hemangiomas
				2		1	1	1	2	2	1	1											X ray skull- normal				6	
				2		1	1	1	2	2	1	1															1	
				2		1	1	1	2	2	1	1			12.5		2.865		1		2	2					7	
				2		1	1	1	2	2	1	1							2		2	2	AVM- doppler				10	
				2		1	1	1	2	1	1	1			12.2	1.91			2	1	2	2		6			9	
41	39	31	28	1	left LL overgrowth	1	1	1	1	2	1	1								1	2	2					7	
				2		1	1	1	2	2	1	1						AVM	2					5			10	
				2		1	1	1	2	2	1	1			14.6	3.78											6	
				2		1	1	1	2	2	1	1															1	
				2		1	1	1	2	2	1	1															1	
				2		1	1	1	2	2	1	1			15.2	3.36											1	
				2		1	1	1	2	2	1	1						no deep involvement						6			8	
				2		1	1	1	2	2	1	1							3	1			doppler- no flow				8	
				2		1	1	1	2	2	1	1															1	
				2		1	1	1	2	2	1	1															6	
29	31	19	20	1	macrocephaly,left limbs	2	2	1	1	2	1	1								3			MRI- leptomeningeal enhanceme				11	MCAP / PPV 5b
				2		1	1	1	2	2	1	1												4			6	
				2		1	1	1	2	2	1	1															1	resolved HOI
				1	webbed neck,brachyceg	2	1	1	2	2	1	1			13.6	3.68											6	
				2		1	1	1	2	2	1	1			10.8	2.6	1.398										1	Involuting HOI
				2		1	1	1	2	2	1	1			9.2	3.22				1			VLM rectosigmoid- MRI				9	
				2		1	1	1	2	2	1	1															6	
				2		1	1	1	2	2	1	1															6	
				2		1	1	1	2	2	1	1			12.1			thrombosed VM							benign angiomatous les		7	thrombosed venous ma
				2		1	1	1	2	2	1	1															6	
				2		1	1	1	2	2	1	1															1	
				2		1	1	1	2	2	1	1			16.7	1.39	4.3										1	
				2		1	1	1	2	2	1	1			10.7	2.93	7.565										1	Involuting HOI
				2		1	1	1	2	2	1	1			11.4	2.16		horse shoe kidney	1	1	2	2	VLM - MRI	6			9	
				2		1	1	1	2	2	1	1															1	
				2		1	1	1	2	2	1	1			9.6	7.34							echo- normal				1	
				2		1	1	1	2	2	1	1			9.2	5.68		abdomen- normal									1	multiple hemangiomas
				2		1	1	1	2	2	1	1							2				arterial flow				1	
				2		1	1	1	2	2	1	1															1	
				2		1	1	1	2	2	1	1															1	
23	22	16	15	2		1	1	1	1	2	1	1											doppler- normal				6	CM + limb hypertrophy
				2		1	1	1	2	2	1	1															6	
				2		1	1	1	2	2	1	1															6	
				2		1	1	1	2	2	1	1			12.7	2.8											8	Congenital lymphedema
				2		1	1	1	2	2	1	1															1	
				1	left UL hypertrophy, lipo	1	1	2	1	2	1	1	1002	2					1	1	2	2	VM, LM, hypoplastic de	6			11	KTS- ?PROS
				2		1	1	1	2	2	1	1					3.8	normal									1	multiple hemangiomas
				2		1	1	1	2	2	1	1															1	
		36	37	1	supernumerary digit,her	1	1	1	2	2	1	1													epidermal nevus		11	epidermal nevus syndro
				2		1	1	1	1	2	1	1	1174	2	12.1	1.87				1	2	1	VM, intraosseous involvement				7	
				1	left UL overgrowth, mac	1	1	1	1	2	1	1	359	1				VM,LM	1		2	2	multiloculated cystic lesions				9	? PROS
				2		1	1	1	2	2	1	1					5.8	no deep involvement									2	
				2		1	1	1	2	2	1	1	229	1					1		2	1	VM				7	
				2		1	1	2	2	2	1	1			15.5			normal									6	
				2		2	1	1	2	2	1	1															1	Involuted hemangioma
				2		1	1	1	2	2	1	1	274	1						1	2	2					7	
				2		1	1	1	2	2	1	1															1	
				2		1	1	1	2	2	1	1							1								8	

KEY TO MASTER CHART

Variable	Variable name	Code
sno	Serial number	
hosp no	Hospital number	
age	Age of the patient	yy --.-- mm
sex	Sex of the patient	1= male, 2= female
info	informant	[1= self, 2= mother, 3= father]
addr	address	[1= north India, 2= south India, 3= Foreign country]
consan	consanguinity	[1= yes, 2= no]
degree	degree of consanguinity	[1= first,2=second,3=third]
rmac	red macule	[1= yes , 2= no]
purpap	purple or dark red papules	[1= yes , 2= no]
rplaq	red plaque	[1= yes , 2= no]
cm-like	cutis marmorata like	[1= yes , 2= no]
ecchy	ecchymotic	[1= yes , 2= no]
cl-ves	clear vesicles	[1= yes , 2= no]
bluish	bluish lesions	[1= yes , 2= no]
og	overgrowth	[1= yes , 2= no]
birth	present at birth	[1= yes , 2= no]
onset	age of onset	mm ###.## dd
course	course of lesion	[1= stable, 2= rapidly progressive, 3= proportionately progressive, 4= involuting]
crying	relationship to crying	[1= nil, 2= prominent]
complication	complications	[1= nil, 2= ulceration, 3=thrombosis, 4= bleeding, 5= oozing, 6= infection]
othercomp	other complications	
exfactor	exacerbating factors	[1= nil, 2= trauma, 3= infection, 4= puberty, 5= pregnancy]
eyesym	eye symptoms	[1= nil, 2= glaucoma,

```
                                    3= blindness, 4= coloboma]

cnssym        CNS symptoms        [1= nil
                                   2= seizures
                                   3= developmental delay
                                   4= stroke]

cvssym        CVS symptoms        [1= no, 2= yes]
maternal      maternal ante n perinatal h/o [1= nil
                                             2= infections
                                             3= drugs
                                             4= CVS
                                             5= PROM]
preterm       preterm delivery    [1= yes, 2= no]
delivery      mode of delivery    [1= Vaginal delivery, 2= LSCS]
birthwt       birth weight        #.## kg
lbw           low birth weight    [1= yes, 2= no]
fho           family history      [1= yes, 2= no]
lestype       type of lesion      [1= vascular tumour
                                   2= vascular malformation]

og            Overgrowth         [1= yes, 2= no]
sign          signs of lesion    [1= nil, 2= compressibility,
                                  3= increased local temperature
                                  4= pulsatile]
others        other cutaneous lesions
mucosa        mucosal involvement [1= involved, 2= not involved]
mlesion       mucosal lesions
numles        number of lesions   [1= single, 2= multiple]
site          sites of lesions
head          head and neck      [1= yes, 2= no]
UL            upper limbs        [1= yes, 2= no]
chest         chest              [1= yes, 2= no]
abd           abdomen            [1= yes, 2= no]
back          back               [1= yes, 2= no]
LL            lower limbs        [1= yes, 2= no]
perineum      perineum           [1= yes, 2= no]
genitalia     genitalia          [1= yes, 2= no]
buttocks      buttocks           [1= yes, 2= no]

length        length of lesion   ##.#cm
width         width of lesion    ##.#cm

circum        circumference      [1=yes, 2= no]

rma        right mid arm circumference      ##cm
lma        left mid arm circumference       ##cm
```

```
rmf         right mid forearm circumference  ##cm
lmf         left mid forearm circumference   ##cm
rmt         right mid thigh circumference    ##cm
lmt         left mid thigh circumference     ##cm
rml         right mid leg circumference      ##cm
lml         left mid leg circumference       ##cm

dysm           dysmorphic features   # [1= yes, 2= no]
dysmtype       dysmorphic feature type

cns            central nervous system [1= normal, 2= abnormal]
eye            eyes                   [1= normal, 2= abnormal]
spine          spine                  [1= normal, 2= abnormal]
hyper          limb hypertrophy       (1= yes, 2= no)
hypo           limb hypotrophy        (1= yes, 2= no)
abdomen        abdomen                [1= normal, 2= abnormal]
cvs            cardiovascular system  [1= normal, 2= abnormal]

ddimval        D-dimer value     #### ng/ml
ddimer         D-dimer           #  1= normal, 2= elevated
Hb             hemoglobin        ##.## gm/dl
platelets      platelet count    #.## lakhs
tsh            TSH               ##.###
usg            ultrasound
doppler        colour doppler scan    [1= slow-flow,
                                       2= high-flow,
                                       3= others]
mri            MRI scan of lesion     [1= slow-flow,
                                       2= high-flow,
                                       3= others]
embryonic      embryonic/lateral marginal vein  [1= yes, 2= no]
phleb          phleboliths                      [1= yes, 2= no]
otherradio     other radiological findings
biopsy         skin biopsy    [1= infantile hemangioma
                               2= tufted angioma
                               3= kaposiform hemangioendothelioma
                               4= capillary malformation
                               5= venous malformation
                               6= lymphatic malformation
                               7= angiokeratoma]

otherbiop      other skin biopsy findings
```

diag	diagnosis	[1= infantile hemangioma 2= RICH 3= NICH 4= tufted angioma 5= kaposiform hemangioendothelioma 6= capillary malformation 7= venous malformation 8= lymphatic malformation 9= mixed venolymphatic malformation 10= arteriovenous malformation 11= others]
Otherdiag	other diagnosis	